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TOTAL THYROIDECTOMY IN DIABETES MELLITUS

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The patient in the following case volunteered to undergo total thyroidectomy. The operation was undertaken with the hope of securing thereby some improvement of his diabetes. His basal metabolic rate was normal beforehand, and there were no symptoms or signs of hyperthyroidism. He fully understood the hazards involved, as well as the uncertainty as to the therapeutic results obtainable. So far as we know this is the first time that the thyroid gland has been completely resected in an uncomplicated case of severe diabetes.†

REPORT OF CASE

The patient was a white man, aged twenty-six years. He came to the clinic May 26, 1933. The history was of severe diabetes of eleven years' duration. A rigidly restricted diet had been followed, with which about 45 units of insulin had been required daily. The patient had had influenza at the age of eleven years, a mild head injury at the age of fourteen years, an attack of some diabetic acidosis and threatening coma in 1929, and dry pleurisy in 1930.

Physical examination gave essentially negative findings. The height was 67 inches (170 cm.), the weight 126 pounds (57 kg.). The thyroid gland was just palpable, symmetrical, and apparently normal There were no symptoms or signs suggesting any abnormality of thyroid function, and the basal metabolic rates were normal (+5 and +2 per cent).

A specimen of urine, collected overnight, contained 1.61 per cent sugar, and no acetone bodies. A specimen of blood taken early in the morning, when the patient was fasting, contained 14.7 gm. of hemoglobin, 429 mg. of sugar and 208 mg. of cholesterol per 100 cc. Leukocytes numbered 6,800 per cubic millimeter of blood. The serologic test of the blood for syphilis, the roentgenologic examination of the thorax, and the electrocardiogram gave negative findings.

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†Dr. H. L. Blumgart has sent us some interesting information regarding a case of diabetes and tuberculosis in which a striking improvement in tolerance was obtained by thyroidectomy. A Jewess, twenty-four years of age and married, had had nonprogressive pulmonary tuberculosis and had required 105 units of insulin daily. In spite of this the urine frequently had revealed large traces of sugar. The diet had contained 140 gm. of carbohydrate, 80 gm. of protein, and 140 gm. of fat. After thyroidectomy, November 15, 1933, the insulin requirement had dropped and by December 19 had reached 45 units. The basal metabolic rate, which before the operation had been normal, had reached −20 per cent by that date; later it had fallen to −30 per cent, and the insulin dose had been still further reduced. In this case great difficulty had been encountered before the operation by the instability of the blood sugar. Although the urine had frequently contained sugar, severe reaction to insulin had developed every few days. After operation this complication was no longer encountered. It is quite possible that total thyroidectomy may prove to be of real usefulness for cases of this "brittle" type.

The patient was allowed to remain ambulatory and was placed on a weighed diet of 2,300 calories. This was served from the diet kitchen. It consisted of 103 gm. of carbohydrate, 59 gm. of protein, and 183 gm. of fat. An arbitrary dose of 10 units of insulin was given three times daily, and complete, twenty-four hour specimens of urine were collected daily. The excretion of glucose on this regimen averaged 36 gm. for each twenty-four hours.

On May 30, 1933, radical thyroidectomy was performed. Each lobe of the thyroid gland was about normal in size and consistency. Practically all of the thyroid was removed, but thyroid tissue was preserved at the hilus of each lobe, equivalent to not more than the size of a split pea. The outside capsule of the gland, near the hilus, was left in order to try to protect the parathyroid glands. The recurrent laryngeal nerves were not injured. The specimen removed was examined microscopically and had the appearance of normal, resting, thyroid tissue. It weighed 10 gm. The postoperative course was uneventful, and the patient left the hospital on the seventh day.

Progressive increase in sugar tolerance, and progressive fall in basal metabolic rate were noted from about the tenth day after operation. An electrocardiogram, twenty-nine days postoperatively, was normal. No signs of parathyroid deficiency were noted at any time. Chvostek's and Trousseau's signs were consistently negative.

At dismissal, thirty days after operation, the diet, consisting as before of 103 gm. of carbohydrate, 59 gm. of protein, and 183 gm. of fat, was tolerated, with only 15 units of insulin. The urine was practically sugar-free on this regimen. The basal metabolic rate was —29 per cent.

At home the patient maintained himself on essentially the same diet and kept an accurate record of insulin used and glycosuria observed. The patient was under the care of his home physician, for whose coöperation we are very grateful. Symptoms of myxedema made their appearance about sixty days after the operation, and 12 grains (0.77 gm.) of thyroid extract were taken orally during a period of four days. The symptoms of myxedema disappeared but whereas before this thyroid extract was taken the daily requirement for insulin was 10 units, it increased to 30 units four days later. Two weeks afterward, administration of thyroid having been stopped, the requirement for insulin was back to 10 units. Thirty days later signs of myxedema reappeared.

The patient returned to the clinic September 13, 1933, with the typical findings of myxedema, tightness of muscles, swelling of the face, dry skin, falling hair, sluggishness, gain in weight, forgetfulness, and sensitiveness to cold. The basal metabolic rates were —33, —35, and —35 per cent. The previous diet was continued, and the urine remained practically sugar-free with doses of 8 to 12 units of insulin daily. Three grains (0.24 gm.) of thyroid extract (Parke Davis & Company) was given orally on the first day and ½ grain (0.032 gm.) each subsequent day. Two days after the initial dose of thyroid extract, the gross evidence of myxedema had disappeared. The requirement for insulin remained around 12 units per day, and the urine, sugar-free.

The patient left for home eight days after his second admission. In a letter dated November 3, 1933, he wrote that he was taking 8 to 10 units of insulin and 1/10 grain (0.006 gm.) of thyroid extract daily. The only thing that bothered him was "trying to dress warm enough to be comfortable when outdoors on a chilly day." He had lost the stiff, aching sensations in his arms and legs. In a letter dated November 23, 1933, he expressed dissatisfaction with the results of the operation. He considered himself lacking in strength and endurance.

COMMENT

The influence of the thyroid gland in diabetes has been known since Dumontpallier, in 1867, reported a case of glycosuria with exophthalmic goiter. As the goiter improved under treatment so did the diabetes.

In 1904, Lorand, in Minkowski's laboratory, noted the disappearance of diabetes of three depancreatized dogs ten days after thyroidectomy. In 1908, Eppinger, Rudinger, and Falta, and in 1909 W. G. MacCallum, performed the same experiment and obtained diminution, but not complete disappearance of glycosuria. Also in 1909, McCurdy performed thyroidectomy on three dogs, leaving the parathyroid bodies intact, and found that

TABLE

TOTAL THYROIDECTOMY IN DIABETES MELLITUS

MALE AGE, 26 YEARS HEIGHT, 170 CM. DIABETES FOR 11 YEARS

Date 1933	Weight, kg.	Diet: Carbohydrates	Diet: Protein	Diet: Fat	Insulin Units	Glycosuria Grade	Basal Metabolic Rate	Comments
OBSERVATIONS BEFORE OPERATION								
May 26	57.2	103	59	183	30	4	....	Sugar excreted 22 gm.
27	....	103	59	183	30	4	+ 5	Sugar excreted 60 gm. Fasting blood sugar 429 mg. Blood cholesterol 208 mg.
28	....	103	59	183	30	4	....	Sugar excreted 13 gm.
29	....	103	59	183	30	4	+ 2	Sugar excreted 48 gm.
TOTAL THYROIDECTOMY, MAY 30, 1933. OBSERVATIONS AFTER OPERATION								
May 31	....	120	0	0	40	1	....	Sugar excreted 2 gm.
June 1	....	84	45	113	45	4	− 9	Sugar excreted 20 gm.
2	....	84	45	113	65	4	0	Sugar excreted 20 gm.
3	....	75	50	160	60	2	+ 2	Sugar excreted 7 gm.
4	....	103	59	183	60	3	....	Sugar excreted 13 gm.
5	....	103	59	183	45	1	+ 6	Dismissed from hospital.
6	....	103	59	183	30	1	....	
7	....	103	59	183	30	1	− 7	
8	57.7	103	59	183	25	1	−12	
9	....	103	59	183	25	1	+ 4	
10	....	103	59	183	20	1	− 1	
11	....	103	59	183	20	1	....	
12	....	103	59	183	25	1	−10	
13	....	103	59	183	20	2	− 7	
14	....	103	59	183	25	1	− 5	
15	....	103	59	183	20	0	−15	Insidious onset of puffiness, pasty appearance of face.
16	....	103	59	183	20	0	−15	
17	....	103	59	183	20	1	−11	
18	....	103	59	183	20	0	....	
19	....	103	59	183	20	1	−13	
20	....	128	58	191	20	1	−14	Fasting blood sugar 8:00 a.m. 400 mg.; 11:30 a.m. 341 mg.; 4:30 p.m. 91 mg. Blood cholesterol 303 mg.
21	....	128	58	191	20	2	−14	
22	....	128	58	191	20	0	−14	
23	....	128	58	191	20	1	....	
24	....	128	58	191	20	1	−19	
25	57.7	103	59	183	15	0	....	
26	....	103	59	183	15	1	−12	
27	....	103	59	183	10	1	−21	Patient dismissed to home.
PATIENT HOME JUNE 28, 1933, TO SEPTEMBER 13, 1933								
Aug. 1	59.5	103	59	183	10	0–1	....	Patient complains of swelling of face and extremities, coldness and muscular stiffness. Received thyroid 3 grains daily Aug. 1 to Aug. 4. Insulin requirement increased to 30 units Aug. 5.
5	....	103	59	183	30	1	....	
18	....	103	59	183	10	0	....	
26	....	103	59	183	10	0	....	
SECOND PERIOD AT CLINIC, SEPTEMBER 13, 1933, TO SEPTEMBER 21, 1933								
Sept. 13	....	....	....	....	....	....	....	Symptoms of myxedema evident.
14	59.5	103	59	183	....	....	−32	Fasting blood sugar 100 mg. cholesterol 340 mg., and CO_2 combining power 57.
15	....	....	....	....	....	....	−35	
16	....	....	....	....	12	0	−35	
17	....	....	....	....	8	0–1	....	Desiccated thyroid gland, 3 grains.
18	....	....	....	....	4	2	....	Desiccated thyroid gland, ½ grain.
19	....	....	....	....	21	1	....	Desiccated thyroid gland, ½ grain.
20	....	....	....	....	12	1	−35	Desiccated thyroid gland, ½ grain.
21	....	....	....	....	10	0	−32	Desiccated thyroid gland, ½ grain. Disappearance of gross features of myxedema.

a certain amount of dextrose, which before the operation caused glycosuria, would not do so after the operation.

In 1920 and 1921, Friedman and Gottesman reported a series of experiments in which the thyroid arteries were ligated and thyroidectomy performed on depancreatized diabetic dogs, concluding that removal of the thyroid glands of diabetic dogs seemed to check the glycosuria, provided tetany did not occur. The experiments were not very satisfactory because of the frequent development of tetany. One experiment (Friedman and Gottesman's dog number 100), uncomplicated by tetany, was the following:

The dog was a male, weighing 14 kg., and was subjected to partial pancreatectomy January 12, 1921. The urine subsequently contained from 2 to 3 per cent of sugar. January 19, both inferior thyroid arteries were ligated, and on January 26, complete thyroidectomy was performed; the parathyroid bodies were spared. The urine showed no sugar on the following day and continued sugar-free. February 5, with the blood sugar at 95 mg. per 100 cc., an additional 3.4 gm. of pancreatic tissue was removed, with no change in urinary findings. February 9, the blood sugar was 86 mg. On this day, 150 gm. of glucose was introduced by the stomach tube. Tests for urinary sugar remained negative. On May 9 what remained of the pancreas, amounting to 10 gm., was removed. The urine continued negative for sugar until May 14, when the intestines prolapsed through the wound, and the dog died. Necropsy revealed complete absence of pancreatic tissue. The value for blood sugar was 66 mg. per 100 cc. before the last pancreatectomy, and the weight was 15.9 kg. The diet was liberal, consisting of meat, bread and water.

In 1922 Allen reported the results of thyroidectomy on four depancreatized diabetic dogs. He concluded that deficiency of thyroid may partially or wholly suppress diabetic glycosuria and hyperglycemia, but that the effect is the result of injury or cachexia and that there is no indication that the intrinsic severity of the diabetes was lessened. Glucose tolerance tests disclosed in each instance increased sugar tolerance, but the dogs became rapidly cachectic and died.

The objections to these experiments are great. It is difficult to perform total thyroidectomy on dogs without injuring or removing the parathyroid bodies, and the development of tetany has a disastrous effect on the diabetes, as the work of Friedman and Gottesman showed. Absence of the external pancreatic secretion seriously impairs nutrition. Insulin was not available at the time the experiments were performed, and with the one exception the dogs used were in a serious state of malnutrition by the time they were subjected to thyroidectomy.

The only report of thyroidectomy for diabetes in man that we can find in the literature is that of G. W. Crile in 1915. An excerpt from this paper reads as follows:

"To reduce the kinetic drive in a diabetic who could not be rendered sugar-free during a six-months period of medical treatment, a partial thy-

roidectomy, a ligation of the thyroid vessels, a division of the sympathetic nerves, and the removal of one adrenal gland in successive operations produced a permanent freedom from glycosuria."

On the other hand, there are several reports of marked improvement in cases of diabetes following spontaneous development of a hypothyroid state. For instance, in 1922 Rohdenberg reported an instance of spontaneous disappearance of diabetes; the patient was a Russian Jewess. This patient, at the age of thirty years, had been refused insurance because of glycosuria. During the following ten years the classical signs of diabetes developed, and the woman underwent treatment. At the age of forty years the menopause occurred, glycosuria disappeared, and the patient became able to eat candy without the appearance of sugar in the urine. At the age of forty-three years she died of nephritic coma, and postmortem examination revealed the following: (1) chronic interstitial nephritis; (2) cystic degeneration of the suprarenal glands; (3) almost complete destruction of the secreting alveoli of the thyroid gland, with replacement by connective tissue, and (4) hypertrophy of the islands of Langerhans, which were three to four times normal size in the body of the pancreas.

One of us (Wilder, 1926) has described a case of juvenile diabetes which also illustrated the effect of myxedema in diabetes. Diabetes had developed when a boy was aged sixteen months. The glycosuria had been controlled by a strict diet. Hypothyroidism had developed when he was aged three years, and with it the tolerance had risen to such an extent that a general diet could be taken without excretion of sugar. Thyroid extract then had been administered, but it had been necessary to discontinue this because of intense glycosuria. We saw the boy when he was aged seven years. He was mentally and physically retarded, and the basal metabolic rate was —45 per cent; the value for blood sugar was 120 mg. per 100 cc. The urine was free from sugar. Thyroid extract was administered, and, although the diet was restricted, glycosuria appeared when the basal metabolic rate reached —10 per cent.

Weinstein recently has reported on the infrequency of coexisting diabetes and myxedema. He found only ten reported cases and in the files of The Johns Hopkins Hospital from 1920 to 1931 only two records of cases. In one of the two cases thyroid extract caused improvement of the myxedema but activated the diabetes and arteriosclerotic heart disease. In the other, the patient had had myxedema for twelve years. Thyroid extract was administered and diabetes developed shortly thereafter.

It is well established that injected thyroid extract or spontaneous hyperthyroidism frequently produces mild glycosuria in otherwise normal individuals. It is believed that this bears no relation to true diabetes, for it has been shown by several statistical studies that the simultaneous occurrence of true diabetes and hyperthyroidism is accidental. It is also well known that hyperthyroidism markedly aggravates any pre-existing diabetes and that in cases of diabetes complicated by hyperthyroidism tolerance is

much improved by subtotal thyroidectomy. Fitz concluded that the depression of previously elevated metabolism was responsible for this, a view previously expressed by Allen, who showed that other conditions which lowered basal metabolism, such as fasting and wasting diseases, were beneficent in uncomplicated diabetes. Conversely, conditions which increase the basal metabolic rate in uncomplicated diabetes, such as diet high in protein, fever, pregnancy, and epinephrine, intensify the diabetic state. As previously stated, by one of us, the hypothesis of an interrelationship of thyroid and pancreas has not been proved; the facts are fully accounted for by the varying sensitiveness to insulin that attends varying levels of basal production of heat.

Subtotal thyroidectomy for nontoxic states of the thyroid gland in the course of associated diabetes does not modify the intensity of the diabetes. Fitz came to this conclusion from his observations at The Mayo Clinic, and Wilder, and Coller and Huggins confirmed his observation. This is to be expected. There is, as a rule, no significant change in the basal metabolic rate when an eighth to a fourth of a previously hyperfunctioning thyroid gland is left behind. The basal metabolic rates in eighteen such cases reported by Boothby, in 1920, averaged —4 before and —8 after subtotal thyroidectomy for adenoma without hyperthyroidism.

Total thyroidectomy is another matter. Recently, Blumgart, Riseman, Davis, and Berlin reported the therapeutic effect of total ablation of the normal thyroid gland in conditions of congestive heart failure and angina pectoris. The results have seemed to be highly satisfactory. The basal metabolic rates have been depressed to —30 and below, and with the attending diminution of the previously excessive load on the heart congestive failure and angina have been relieved. The patients exhibited the unpleasant symptoms of myxedema when the basal metabolic rate fell below —30 but not otherwise, and minute doses of desiccated thyroid gland, given by mouth, sufficed to hold the rate at or slightly above this critical level. The encouragement provided by their experience, the previous knowledge of the relation of the degree of thyroid activity to the intensity of diabetes mellitus, and the fact that surgical procedures can now be performed in diabetes with complete safety, prompted us to undertake this operation as one offering possible benefit in diabetes. Our report is submitted not so much as a therapeutic suggestion as because of the significance of its bearing on the physiology of the thyroid gland and pancreas.

SUMMARY

1. Total removal of a morphologically normal thyroid gland produced a marked increase in the tolerance of a patient with severe, uncomplicated diabetes mellitus.

2. The increase in tolerance paralleled roughly the decrease in the metabolic rate.

3. Although the patient's tolerance was greatly improved, the remedial result was not sufficient to justify recommending the procedure as a treatment for diabetes. A careful diet, and small doses of insulin, continue to be necessary six months after the total thyroidectomy was performed and the patient complains that sensitiveness to cold, and lack of endurance are so disturbing that the advantage of an improved tolerance is not appreciated.*

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*One year after operation the patient reported by letter that he was comfortable, taking ½ grain (0.032 gm.) thyroid extract (Parke, Davis and Company) daily. The dose of insulin necessary with the dose of thyroid is from 14 to 16 units daily.

THE URINARY EXCRETION OF A DEPRESSOR SUBSTANCE (KALLIKREIN OF FREY AND KRAUT) IN ARTERIAL HYPERTENSION*

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While the explanation of the immediate mechanism causing persistent elevation of blood pressure has in recent years been greatly clarified in terms of increased arteriolar resistance, the underlying factors, with certain exceptions, which regulate arteriolar tonus are not clearly defined. Maintenance of normal blood pressure, together with adequate tissue nourishment, demands a nice physiologic adjustment between cardiac output, circulating blood volume and available vascular bed. Such adjustment conceivably may be mediated through nervous, chemical or hormonal influences acting either singly or in consonance. As regards their influence upon arteriolar tonus, while something is known of the regulatory activities of the nervous system, the possible importance of the chemical and hormonal influences remains obscure and offers a fertile field for investigation. It is probable that the ultimate answer to the question of arterial hypertension will be found in this field, and a large amount of both experimental and clinical study has been undertaken with that end in view. In general, such investigation has evolved along two main lines. The first has been an effort to detect a "warp" in the metabolism of patients with essential hypertension, by the qualitative and quantitative study of the chemical constituents of the tissues, body fluids and excretory products. No constant deviation from the normal has been established. The second line of endeavor has consisted in the evaluation of the physiologic importance of substances of both metabolic and secretory origin which have a direct influence upon the peripheral circulatory apparatus. Those substances which increase arteriolar tonus, of which adrenalin, pituitrin and methylguanadine are examples, have received the most attention. Numerous attempts to establish in patients with hypertension a constant superabundance of such substances, or an abnormal reaction of the vessel walls to them, have been inconclusive and the positive results so exceptional as to preclude trustworthy deductions. The importance of the depressor substances present in the body has received less study; yet, a priori, a disturbance in the balance between pressor and depressor elements, is a reasonable hypothesis by which to explain the pathologic elevation of blood pressure.

With this hypothesis in mind, a study was undertaken to determine quantitatively the urinary excretion in essential hypertension of a depressor substance which is hormonal in nature and which, under experimental con-

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ditions, antagonizes the pressor effect of adrenalin. This report comprises the results obtained in a study of fifty cases. It will be shown that the urinary excretion was materially decreased as compared with that in persons with normal blood pressures.

NATURE OF THE DEPRESSOR SUBSTANCE

Abelous and Bardier (1) in 1903 first called attention to a depressor substance present in urine, which Pribram and Herrnheiser (2), in a later study, found to be retained by a dialyzing membrane. The significance of these investigations was not apparent until Professor E. K. Frey, chief of the surgical clinic of the Medical Academy in Düsseldorf, and his coworkers described, in 1928, the properties of a vasodilator substance which they conceived to be a hormone having to do with the regulation of peripheral circulatory balance. They gave it the name of "Kallikrein." This substance is elaborated in the pancreas (3, 9). It circulates in the blood stream (in combination with an inactivator, a polypeptide probably elaborated in the lymph glands, 4) and is secreted into the urine in an active form, where it may be recognized by a typical reaction upon intravenous injection into an experimental animal, namely, a fall in blood pressure and, very constantly, an increase in pulse pressure (5). The fall in pressure is due to dilatation of the arterioles of the brain, skin, lungs and muscles (6), while the increase in amplitude of cardiac contraction probably results from increased venous return to the right heart (1). The linkage in the circulating blood between this substance and its inactivator depends upon the pH, increase in acid metabolites causing it to be released with resultant vasodilatation (4, 6).

The assumption that it is a hormone is based primarily upon the fact that in pancreeectomized dogs its urinary excretion is decreased 80 per cent, whereas its excretion is not influenced by the production of pancreatic fistula (3). Ablation of the remaining endocrine glands is without effect (7). However, further studies are necessary to establish it definitely as a secretion of an endocrine gland. The term "hormone" will be used advisedly pending such confirmation.

A unit, definded as that amount which injected intravenously into a dog causes an increase in amplitude of cardiac contraction of one minute's duration (5), is found in from 2 to 20 cc. of human blood after digestion by Papain and dialysis, and in an active form in approximately 5 cc. of human urine (6, 8). While extracts of many organs may contain traces of this substance (9), Frey states that its pharmacologic behavior sharply differentiates it from histamine, choline or acetylcholine. It does not contain urea, uric acid, creatinine, indican, indole or skatol (5). We have likewise found that it does not owe its activity to adenosine, adenylic acid, or glycocyamine—substances which have somewhat similar physiologic properties and which might be present in urine (10). This evidence is briefly as follows: The hormone is nondialysable; its physical behavior is that of a

colloid; the greater part of it is quickly destroyed by heat, strong acid or alkali. It is further distinguished from adenosine and adenylic acid by the fact that it gives a negative test for pentose and does not produce heart block on intravenous injection into the guinea pig, a supposedly specific test for these substances (11). Moreover, the physiologic response upon which the identification of the hormone rests, namely, the increase in pulse pressure due primarily to a fall in the diastolic blood pressure level does not result from the injection of any of the substances mentioned, nor, with one possible exception to be commented upon later, from the injection of any of the usual urinary constituents.

The effect of the hormone upon arteriolar tonus may in part be due to the fact that it is an adrenalin antagonist. We have found that the simultaneous intravenous injection of a concentrated preparation of this substance and adrenalin in the rabbit obviates the usual pressor response caused by the latter (Fig. I), and that physiologic doses of the one are

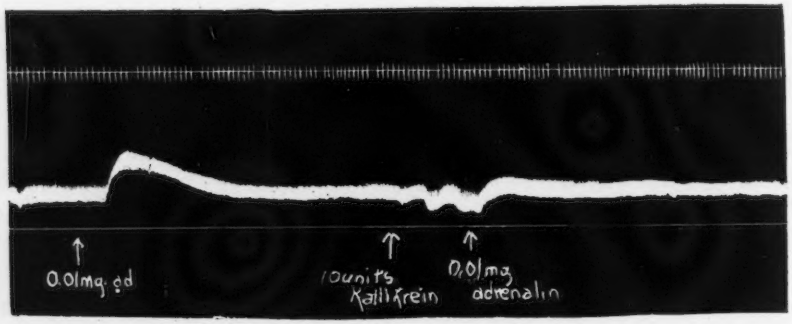

Figure 1. Antagonism of the adrenalin pressor response by kallikrein. The arrows indicate intravenous injection. Time in 5 seconds.

closely balanced by similar doses of the other (i.e., 0.01 mg. adrenalin is neutralized by 5 to 10 times the minimal physiologic dose of the hormone). The hyperglycemia resulting from adrenalin is not affected. This points to the arterioles as its primary and probably sole seat of action. We have found that the substance has no demonstrable effect upon the heart muscle as studied in perfusion experiments performed upon the rabbit heart, and does not cause any alteration in the electrocardiogram of the intact animal. It does, however, dilate the coronary arteries.

It is evident from the foregoing that another substance, possibly a hormone, must be added to those already known to exert a regulatory action upon arteriolar tonus. The fact that it may oppose or balance in the body the most powerful pressor substance of which we have knowledge should arouse an interest in the evaluation of its physiologic importance. Since its presence in the urine can be readily detected, an attempt to determine quantitatively its urinary excretion under normal circumstances and in a

disease state characterized by altered arteriolar tonus was considered to be a worthwhile method of approach to the problem.

CLINICAL MATERIAL

The patients studied were selected on the basis of elevated blood pressure in the absence of present or preceding inflammatory renal disease as determined by the history, repeated examinations of the urinary sediment and, in most cases, by the study of the renal function. Patients in the malignant phase of essential hypertension were excluded. By elevated blood pressure is meant a sustained systolic pressure of 150 mm. Hg., or over, in individuals under 40 years of age, and a pressure exceeding 160 mm. in persons over this age. Most of these patients had complaints referable entirely to the cardiovascular apparatus, but in some there were complicating minor illnesses. The control series consisted of medical students and patients with minor illnesses, having blood pressures that were within a normal range.

METHOD OF DETERMINATION

Grown rabbits were used as test objects. Under sodium amytal anesthesia, the carotid blood pressure was registered on a smoked drum by means of a Hürthle membrane manometer. The response of each animal was calibrated by the intravenous injection of a test solution containing 10 units of the hormone per cc., a unit being the amount sufficient to cause a minimal response, namely, an increase in pulse pressure lasting 3 to 4 minutes, together with a slight fall in blood pressure (Fig. 2). The use of

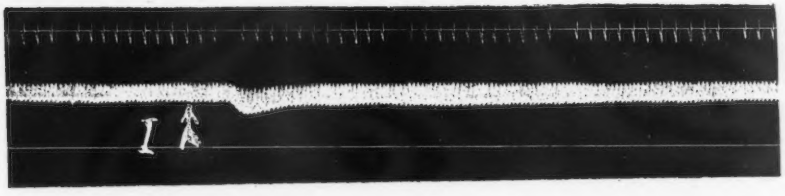

Figure 2. Action of the minimal physiologic dose. Note slight widening of the amplitude of cardiac contraction.

a standard test solution was indispensable, due to great variation in the minimal dose from animal to animal. All results were calculated on the basis of comparative strengths with the standard solution. The response of the same animal to repeated doses was quite constant, but the precaution was observed of recalibrating the animal's response at intervals during the determinations.

The urine to be tested was an accurately timed 12-hour night specimen, and the determination in each instance was made on the following day. The untreated urine was injected into the external jugular vein of the rabbit and the amount necessary to cause the typical minimal response was determined. Twelve rather than 24-hour specimens were examined because,

at the beginning of this work, it was not known whether the hormone would deteriorate upon standing. Subsequent study has shown that, using the usual urinary preservatives, the hormone content will not be changed appreciably over a period of several days within the pH range encountered in

TABLE 1

KALLIKREIN EXCRETION IN PERSONS WITH NORMAL BLOOD PRESSURE

GROUP I—20–30 YEARS OF AGE

Name	Age	Sex	Diagnosis	No. of Determinations	CC. Urine (12 Hour) Night)	Units Kallikren in 12 Hours	Units Kallikren per 1.0 cc. Urine
A. L.	24	♂	Normal	5	Av. 780	Av. 2400	3.07
D. C.	24	♀	Scoliosis	1	685	5500	8.02
N. F.	24	♂	Normal	1	575	4600	8.00
J. A.	25	♂	Normal	1	725	1800	2.48
W. H.	25	♂	Normal	2	Av. 475	Av. 5600	11.78
F. H.	25	♂	Normal	1	1150	11500	10.00
J. S.	25	♂	Hypothyroid	1	645	3200	4.96
D. P.	26	♂	Normal	1	355	3500	9.80
M. A.	28	♀	Normal	1	195	2700	13.84
F. B.	30	♂	Normal	2	Av. 575	Av. 3900	6.78
A. E.	30	♂	Normal	4	Av. 610	Av. 5900	9.67
F. B.	31	♂	Duodenal Ulcer	1	1640	2100	1.21
M. G	35	♂	Post-Op. Appendix	1	570	2900	5.07
A. S.	35	♀	Normal	1	790	1600	2.02
A. B.	38	♂	Normal	2	775	4500	5.80
D. M.	39	♀	Angina Pectoris (?)	1	270	1900	7.03
L. M.	39	♂	Tbc. (Healed)	1	490	1100	2.24
Total 17				Total 27	Av. 665±73	Av. 3800±680	Av. 5.7±0.9

GROUP II—40–59 YEARS OF AGE

H. I.	40	♂	Pneumonia (Convales.)	1	270	600	2.22
F. N.	41	♀	Normal	1	1045	2100	2.00
F. N.	43	M	Normal	1	1060	3200	3.01
F. P	43	♂	Hypothyroid	1	710	3500	4.92
S. V. W.	43	♀	Normal	1	650	2100	3.23
B. P.	44	♀	Normal	1	495	2800	5.65
G. F.	46	♂	Neurosis	1	945	3900	4.12
B. K.	48	♀	Extrasystoles	1	800	1800	2.25
C. C.	48	♂	Fractured Leg	1	480	1600	3.33
R. B.	50	♂	Normal	1	480	6200	12.90
C. C.	52	♀	Normal	1	1180	5600	4.74
H. O.	52	♂	Pneumonia	1	640	2700	4.21
C. C.	52	♂	Normal	1	1675	1800	1.07
B. B	55	♀	Anal Eczema	1	355	1100	3.09
G. K.	55	♂	Hernia	1	1395	7000	5.01
S. S.	55	♀	Diabetes	1	340	3400	10.00
E. S.	56	♂	Iritis	1	2800	3600	1.28
W. H.	56	♂	Diverticulitis	1	630	2700	4.28
R. H.	56	♂	Gastric Ulcer	1	970	2600	2.68
R. N.	58	♀	Normal	1	850	3400	4.00
E. D.	58	♀	Rheumatic Heart Dis.	1	500	450	0.90
M. M.	58	♂	Mitral Stenosis	2	Av. 900	Av. 1500	1.66
F. S.	59	♀	Rheumatic Heart Dis.	1	730	1825	2.50
Total 23				Total 24	Av.865±113	Av. 2773±346	Av. 3.2±0.6

GROUP III—60 YEARS AND OVER

C. H.	60	♂	Normal	1	905	2100	2.32
F. B.	61	♂	Colitis	1	1030	1955	1.89
R. R.	63	♂	Arteriosclerosis	2	Av. 710	Av. 3455	4.86
J. W.	63	♂	Cardiac Decomp	1	870	520	0.59
C. R.	63	♀	Hypothyroid	1	265	530	2.00
D. S.	67	♂	Angina Pectoris	1	685	1165	1.70
C. T.	68	♂	Normal	1	395	505	1.51
A. P.	68	♀	Gastric Ulcer	1	1210	1955	1.61
T. M.	69	♂	Duodenal Ulcer	1	960	1540	1.60
E. D.	72	♀	Ca. Stomach	1	450	1485	3.29
Total 10				Total 11	Av. 748±95	Av. 1530±286	Av. 2.1±0.4

urine. For purposes of comparison, the results are reported throughout in terms of nocturnal 12-hour excretion. The comparison between day and night excretion will be commented upon later.

RESULTS

Kallikrein Excretion in Persons with Normal Blood Pressure. It was found that the urinary excretion of this substance bears a rough but definite correlation with the age of the individual, decreasing with advance in years. In Table 1 are given the individual determinations, together with other pertinent data. An arbitrary division into age groups was made for the purpose of comparison with the hypertension series. It will be noted that the average 12-hour excretion drops from a figure of 3800 ± 680 units in persons under 40 years of age to a figure approximately 1,000 units less than this (2773 ± 346) in persons up to 60 years of age, and that there is a drop of similar magnitude (to 1530 ± 286 units) in the average excretion of this substance in persons of 60 years or older. It is also apparent that the hormone excretion is independent of the urine volume, as shown by the number of units per cc. of urine, and that this average decrease in excretion is not due to a decreased average urine volume in the older age groups. There is a large variation in excretion amongst members of the same age group which apparently is not influenced by the sex of the individual. Repeated determinations upon the same individual likewise have shown a large variability in the amount of the hormone excreted from day to day, but in general this variation has not exceeded that encountered amongst different members of the same age group. The factors that may possibly influence the excretion of this substance in the individual instance will require further study. In any event, they should be equally operative amongst most or all of the individuals comprising this series and should not vitiate the results of a comparison with another series of individuals of the same age who differ in that their blood pressures are elevated.

Kallikrein Excretion in Persons with Elevated Blood Pressure. The results obtained in the hypertension series are given in Table 2, and the average excretion in each age group of both series is compared in Table 3. As would be expected, the greatest number of persons with elevated blood pressures fall in the oldest age group. Only seven patients less than 40 years of age and having hypertension not associated with inflammatory renal disease were available for this study.

It is apparent that the average urinary excretion of the hormone by the patients with hypertension is materially less than the excretion by the patients with normal pressures. For the persons under 40 years of age, the difference averages 1695 ± 751 units (or 3.0 ± 0.9 units per cc. of urine); for those under 60 years, 1333 ± 424 units (or 1.3 ± 0.8 units per cc. of urine); and for those over the age of 60, 635 ± 299 units (or 0.6 ± 0.4 units per cc. of urine). Statistical analysis shows that the difference in the 12-hour excretion in each of the three age groups is significant and, taken

TABLE 2

KALLIKREIN EXCRETION IN PERSONS WITH ESSENTIAL HYPERTENSION

GROUP I—20–39 YEARS OF AGE

Name	Age	Sex	Average Blood Pressure	No. of Determinations	CC. Urine (12 Hour) Night)	Units Kallikren in 12 Hours	Units Kallikren per 1.0 cc. Urine
M. T.	25	♀	165/95	2	Av. 525	Av. 1765	3.36
A. W.	26	♀	150/90	7	Av. 800	Av. 1540	1.92
D. A.	27	♀	170/100	1	245	810	3.30
A. A.	29	♀	160/85	2	Av. 1295	Av. 2800	2.16
M. C.	29	♂	160/90	1	635	3175	5.00
J. Y.	31	♀	160/90	1	1435	2300	1.60
G. E.	37	♂	190/124	1	840	2345	2.79
Total 7				Total 16	Av. 826±158	Av. 2105±324	Av. 2.7±0.4

GROUP II—40–59 YEARS OF AGE

E. M.	41	♀	170/110	1	950	3610	3.80
D. A.	42	♂	190/115	1	1060	4130	3.89
E. G.	43	♀	170/100	1	705	985	1.39
M. D.	43	♀	180/100	1	715	1430	1.90
W. W	44	♂	240/170	1	910	2100	2.30
G. L.	44	♂	180/100	1	785	745	0.94
A. E.	48	♂	188/110	1	600	1500	2.50
T. F.	49	♂	180/110	1	470	705	1.50
N. W.	49	♀	170/90	1	530	475	0.89
S. K.	50	♀	215/130	1	390	665	1.70
W. R.	53	♂	170/95	1	495	990	2.00
E. F.	54	♀	200/105	1	865	1300	1.50
A. F.	55	♀	170/100	1	830	1080	1.30
G. L.	56	♀	180/100	1	620	1430	2.30
A. H.	57	♂	150/110	1	550	1295	2.35
J. K.	58	♂	170/100	1	775	1240	1.60
E. C.	59	♀	180/110	1	1040	835	0.80
Total 17				Total 17	Av. 726±47	Av. 1440±244	Av. 1.9±0.2

GROUP III—60 YEARS AND OVER

A. F.	60	♀	175/95	1	375	415	1.10
A. C.	60	♀	190/110	1	565	1185	2.08
M. H.	61	♀	180/100	1	415	705	1.69
E. N.	62	♀	160/110	1	520	1295	2.49
C. R.	63	♂	190/110	1	255	410	1.56
G. Y.	65	♂	160/90	1	465	1720	3.69
C. G.	65	♀	180/80	1	865	865	1.00
T. P.	65	♂	200/150	1	910	220	0.24
J. L.	65	♀	200/90	1	1180	1415	1.18
S. B.	66	♀	200/100	1	675	1150	1.70
K. N.	66	♀	210/90	1	190	380	2.00
G. T.	67	♂	260/150	1	1750	875	0.60
E. L.	67	♀	160/85	1	435	325	0.74
V. W.	67	♀	200/100	1	510	610	1.19
P. M.	69	♀	180/100	2	Av. 1260	Av. 1478	1.17
J. C.	69	♀	200/100	1	245	810	3.30
H. McA.	70	♂	160/100	1	675	1350	2.00
P. M.	71	♂	170/100	3	Av. 550	Av. 1495	2.71
T. W.	73	♀	170/110	1	275	550	2.00
F. J.	73	♀	200/90	1	290	840	2.89
M. M.	74	♀	160/90	1	430	1210	2.81
C. C.	75	♂	180/90	1	330	725	2.19
F. E.	79	♂	220/120	2	Av. 510	Av. 920	1.80
L. C.	79	♀	200/100	1	525	785	1.30
F. C.	80	♂	170/100	1	945	1225	1.29
H. B.	82	♂	180/90	1	625	340	0.54
Total 26				Total 30	Av. 606±58	Av. 895±89	Av. 1.5±0.2

as a whole, quite conclusive of a lessened Kallikrein excretion in this series of hypertensive patients.

One other point should be noted. We believe that, had we determined the Kallikrein excretion over a period of 24 hours rather than for a 12-hour night period only, these differences would have been more pronounced. A

TABLE 3

AVERAGE EXCRETION OF KALLIKREIN COMPARED ACCORDING TO AGE

	50 Persons With Normal Blood Pressure			50 Persons With Elevated Blood Pressure		
Age Group	20-39 Yrs.	40-59 Yrs.	60 Yrs. and Over	20-39 Yrs.	40-59 Yrs.	60 Yrs. and Over
Number of Patients	17	23	10	7	17	26
Number of Determinations	27	24	11	16	17	30
Average cc.'s Urine per 12 Hour Night	665±73	865±113	748±95	826±158	726±47	606±58
Average Units Kallikrein Excreted in 12 Hours	3800±680	2773±346	1530±286	2105±324	1440±244	895±89
Average Units Kallikrein per 1.0 cc. Urine	5.7±0.9	3.2±0.6	2.1±0.4	2.7±0.4	1.9±0.2	1.5±0.2

TABLE 4

COMPARATIVE DAY AND NIGHT EXCRETION OF KALLIKREIN

Group 1 Normal Blood Pressure				Group 2 Elevated Blood Pressure			
Case No.	Day No. Units	Night No. Units	Difference No. Units	Case No.	Day No. Units	Night No. Units	Difference No. Units
1	280	1600	680	1	1120	965	155
2	5080	6500	1420	2	850	730	120
3	2230	1665	565	3	395	2300	1905
4	3905	3885	20	4	1000	1230	230
5	1485	1125	360	5	685	1415	730
6	3990	3430	560	6	690	1080	390
7	3935	1275	2660	7	2140	840	1300
8	2375	2040	335	8	915	2440	1525
9	6560	3945	2615	9	1180	1570	390
10	2200	2225	225	10	1280	985	295

study of the night and day excretion (Table 4) shows that there is a considerable variation in the amounts of Kallikrein excreted during these periods. Persons with normal blood pressures tend to excrete more during the day than during the night, whereas in persons with elevated pressures a converse tendency is apparent. In some of the latter there was a comparatively large output during the night with a decrease far below this figure during the day (Group 2, Cases Nos. 3, 5 and 8). If these tendencies are true for a large series, a study of 24-hour excretion, by taking them into account, should demonstrate more clearly the decreased urinary output of Kallikrein by patients with hypertension.

The Heat Stabile Fraction. It has been mentioned that the hormone is heat labile. We have found that heating a test solution for five minutes at 100 degrees Centigrade resulted in an 80 per cent loss of potency. During the course of this study a paper appeared by Wolheim and Lange (12) dealing with the quantitative estimation of a heat stabile substance in the urine of normal individuals and of those with hypertension. After being boiled for five minutes, the urine was injected intravenously into rabbits or cats with resultant fall in blood pressure and increase in pulse pressure. The published tracings are identical with those which we have obtained with the hormone. In 122 determinations on 38 patients with essential hypertension, a minimal amount or total absence of the substance was

demonstrated. These workers concluded that because of the property of heat stability they were dealing with a substance distinct from Kallikrein. Since the method of identification is identical, it became necessary to determine if the apparent decreased Kallikrein excretion in our hypertensive patients was due to a lessened amount of what may be termed the heat stabile fraction. The urinary excretion of both of these substances was determined in a series of 20 patients with normal blood pressure, and a like number with hypertension. The results are listed in Table 5. The figures

TABLE 5

COMPARATIVE URINARY EXCRETION OF HEAT-LABILE AND HEAT-STABILE FRACTIONS IN 12 HOURS

Group 1 Normal Blood Pressure				Gr up 2 Elevated Blood Pressure			
Case No.	Unstabile (Units)	Stabile (Units)	Total (Units)	Case No.	Unstabile (Units)	Stabile (Units)	Total (Units)
1	4620	1980	6600	1	910	455	1365
2	810	675	1485	2	354	0	354
3	530	0	530	3	408	0	408
4	3060	340	3400	4	706	0	706
5	2989	441	3430	5	255	226	481
6	294	831	1125	6	325	0	325
7	3385	500	3885	7	70	955	1025
8	1265	315	1580	8	661	147	808
9	2380	1020	3400	9	1534	186	1720
10	2633	97	2730	10	1302	128	1430
11	1295	550	1845	11	1080	270	1350
12	2773	2772	5545	12	1840	160	2000
13	671	864	1535	13	723	117	840
14	5952	288	6240	14	1500	0	1500
15	4932	548	5480	15	830	250	1080
16	5580	1395	6975	16	870	116	986
17	3365	185	3550	17	1189	226	1415
18	2523	297	2820	18	849	376	1225
19	1676	404	2080	19	1579	716	2295
20	903	237	1140	20	392	0	392
Average...	2581±548	687±153	3264±442	Average...	869±110	216±56	1954±227

listed in the column headed "Unstabile" were arrived at by subtracting the number of units present after boiling from the total number of units in the untreated urine. In general, there was a rough correlation between the excretion of these two fractions in both series of patients. The average number of stabile units (687±153 units, normal pressure; 216±56 units, hypertension) was approximately one-quarter as much as the unstabile units (2581±548 units, normal pressure; 869±110, hypertension). The average excretion of each fraction was decreased in the hypertension series to a parallel extent as compared with the average normal, namely, heat unstabile, average decrease 66 per cent; heat stabile, average decrease 68 per cent. It can be concluded that the decreased excretion of the hormone previously described does not depend wholly upon a lessened output of the heat stabile substance. Individual exceptions to this have been encountered. In one hypertension patient not included in the table, the total number of units in untreated urine excreted in 12 hours was 4130, but none of the heat stabile substance was present. Repetition of the determination at a later

date gave similar results. Conversely, a satisfactory excretion of the heat stabile substance may occur in the presence of a limited output of the heat labile fraction (Group 2, Case No. 7 in the table). Also Cases Nos. 10 and 17 of Group 1 might be mentioned, in whom apparently the excretion of the heat stabile fraction alone was depressed.

DISCUSSION

That there may exist a disturbance in balance between pressor and depressor elements in arterial hypertension is suggested by the recent work of several observers. Bohn and Holm (13), working in Volhard's clinic, have demonstrated, by the use of ultrafiltration and also alcoholic extraction, the presence in excess of a pressor principle, which they tentatively identify with the secretion of the posterior lobe of the pituitary gland, in the blood and urine of patients with "pale" (i.e., nephritic, malignant) hypertension. This was not true in patients with essential hypertension. Lange (14) believes that in nephritic hypertension there is retention in the body, with lessened urinary concentration, of a depressor substance which is identified (15) as a di-guanidin compound. Conversely, in essential hypertension this substance slips past the renal barrier in an increased amount, leaving a lessened concentration in the blood stream as compared with the normal. Major (16) has reported a high percentage of positive color tests for guanidin compounds in the blood of persons with hypertension and is led to believe that a pressor guanidin derivative may be present in excess in such instances. We (17) have likewise offered evidence to suggest that a pressor principle may exist in the circulating blood of such individuals. Dicker (18) has recently injected alcoholic extracts of urine into an experimental animal. Extracts of normal urine gave a pronounced pressor response, while extracts of nephritic urine caused a fall in blood pressure. In essential hypertension, neither a pressor nor depressor effect could be demonstrated in this manner.

It is impossible to integrate such observations, with their varying implications, into one definite physiologic concept. Extreme caution in the interpretation of data of this character is obviously indicated. To be valid, conclusions drawn from a decreased amount of a urinary constituent, as reflecting conditions in the pre-kidney, must postulate a normal renal function, eliminating the possibility of simple retention. In the present study we have attempted to evaluate carefully this factor, excluding patients in whom renal impairment was demonstrable. In a number of such patients, however, the excretion of Kallikrein was not less than that encountered in patients with hypertension and presumably normal kidney function (see Table 6). However, in several instances of glomerulonephritis and malignant hypertension with renal failure, the concentration of urinary Kallikrein was extremely low. Since simultaneous determination of the Kallikrein level in the blood was impossible, one cannot say whether or not a simple retention existed. If the amount of Kallikrein in

TABLE 6

URINARY EXCRETION OF KALLIKREIN IN PATIENTS WITH AND WITHOUT RENAL IMPAIRMENT

Name	Age Years	Sex	Tests of Renal Function							Units Kallikrein in 12 Hours
			Urinalysis			P. S. P.	Urea Clearance	Volhard Water Test		
			Albumin	Casts	Cells			Concentration Sp. Gr.	Dilution Sp Gr.	
GROUP 1—GOOD KIDNEY FUNCTION										
E. G.	43	♀	0	0	0	....	55% of Normal	1.028	1.008	980
M. D.	43	♀	0	0	0	55%	39% of Normal	1.032	1.010	1430
W. W	44	♂	0	Occas. Hyaline	0	55%	.... of Normal	1.029	1.010	2090
S. K.	50	♀	Trace	0	0	70%	43% of Normal	1.026	1.009	665
A. F.	55	♀	0	0	W. B. C. 7/h d. f.	65%	.... of Normal	1.030	1.005	1080
J. K.	58	♂	+	0	0	60%	109% of Normal	1.025	1.007	1240
E. C.	59	♀	Trace	Occas. Hyaline	0	60%	.... of Normal	1.026	1.010	835
A. C.	60	♀	Trace	0	0	60%	115% of Normal	1.028	1.010	1185
M. H.	61	♀	0	0	0	55%	.... of Normal	1.025	1.006	705
K. N.	66	♀	0	0	0	100%	76% of Normal	1.028	1.0 5	385
E. L.	67	♀	0	0	0	50%	62% of Normal	1.026	1.011	330
										Average 993 ± 409
GROUP 2—IMPAIRED KIDNEY FUNCTION										
A. L.	48	♂	++	Hyaline Gran. +	0	25%	64% of Normal	1.020	1.010	1500
W. R.	53	♂	+	Occas. Hyaline	0	45%	56% of Normal	1.024	1.009	990
E. F.	54	♀	0	0	0	50%	50% of Normal	1.015	1.004	1300
G. T.	67	♂	++	Hyaline ++	R. B. C. Occas.	25%	63% of Normal	1.020	1.012	875
J. C.	69	♀	+	Occas. Hyaline	0	50%	54% of Normal	1.024	1.006	810
M. M.	74	♀	Trace	0	W. B C. 5/h. d. f.	55%	35% of Normal	1.020	1.007	1210
F. E.	79	♂	+	Hyaline +	0	25%	55% of Normal	1.020	1.007	920
										Average 1229 ± 129

the urine were primarily a reflection of renal activity, some degree of correlation should exist between it and the volume of urine excreted. Such a phenomenon was not observed in this series of patients, but the question demands further study. It is our impression, from the data at hand, that the excretion of Kallikrein, within fairly wide limits, is not strictly governed by the functional capacity of the kidneys.

In the foregoing we have spoken of a decreased excretion of Kallikrein in the patients with hypertension. Another possibility remains to be considered. It is conceivable that the amount of urinary Kallikrein is fairly constant, but that there is excreted into the urine a varying amount of pressor substance, or substances, which serves partially to inactivate the biologic response upon which its identification rests. In other words, the depressed excretion of Kallikrein in these patients may be apparent in that we have actually measured an increased amount of a physiologically antagonistic principle. The experiments of Bohn and Holm and of Dicker indicate that a pressor substance, or substances, actually exist in the urine. The experimental procedures of Bohn and Holm probably, and of Dicker certainly, served to remove the Kallikrein from their urine samples, but their results, with the possible exception of the first named investigator, cannot be satisfactorily explained on the basis of such an assumption alone. Their results stand in conformity neither with ours nor with each other's. We feel that in using untreated urine, with the avoidance of possible mutations due to chemical or physical procedures, a disturbance in balance between pressor and depressor elements has been more surely indicated and can hardly be without physiologic significance. We hope that confirmation of this study will justify such a conclusion.

SUMMARY

1. The chemical and physiologic properties of a vasodilator substance present in urine are reviewed. Evidence is given which indicates that the substance is probably a hormone elaborated in the pancreas and has to do with the regulation of arteriolar tonus, possibly by antagonizing the pressor effect of adrenalin.

2. It was demonstrated that the average rate of urinary excretion of this substance in 50 persons with essential hypertension was materially less than the rate of excretion in individuals of the same age with normal blood pressure.

3. It is believed that the lessened urinary output in this series of hypertension patients cannot be adequately explained by the assumption of an altered renal function but is a reflection of disturbance in the pre-kidney.

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THE PRODUCTION OF TESTICULAR DESCENT WITH THE WATER-SOLUBLE (ANTERIOR PITUITARY-LIKE) FRACTION OF PREGNANCY URINE

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Until relatively recent times persons lacking completely descended testes were subjected to surgical treatment for the alleviation of this condition. Those acquainted with such procedures will recall the difficulties met with and the incomplete results incident to the process of "lengthening the cord."

In 1930 Schapiro subjected several adolescent boys with incompletely descended testes to medical treatment by employing Aschheim and Zondek's prehormone. This led to a fair degree of success. Since then Engle (1932a) succeeded in producing complete testicular descent in immature monkeys (Macacus rhesus) by the use of water-soluble fractions of pregnancy urine and anterior pituitary extract. By this method of treatment the cord lengthened naturally.

In the successful instances mentioned above, however, the testes had already entered the inguinal canals before treatment was begun. Since testicular descent within the canal is believed by some to occur as a passive phenomenon as this gland enlarges and since the internal abdominal ring is normally closed in the human and macaque at birth (Wislocki, 1933) it is questionable from these reports whether descent would occur if the testes were intra-abdominal prior to treatment.

This question has fortunately become answerable since a patient afflicted with dystrophia adiposo-genitalis and in whom the testicles were still bilaterally intra-abdominal presented himself for treatment. The child was treated with the water-soluble fraction of pregnancy urine and the results obtained in this case were then confirmed on four groups of albino rats.

The extract used was prepared by the Squibb biological laboratories by a modification of the Zondek and Aschheim process.* The concentrated extract is dissolved in glycerin, physiologically assayed and passed through a Berkfeld filter. Each cubic centimeter is standardized to contain 1250 rat units (250 Zondek-Aschheim mouse units). Before being used, this glycerin solution was diluted with four parts of distilled water.

CLINICAL CASE

The patient, a white male, aged 10½ years, had a family history which was entirely irrelevant. He was a full term child weighing 8 lbs. 14 ozs. at birth

*The complete process is described by E. R. Squibb & Sons in a pamphlet contained in each package of their Follutein.

which required the aid of high forceps. He sat up at 5½ months, stood at 11 months, talked at 15 months and walked at 16 months. The history concerning dentition was unobtainable. His appetite during infancy was noticeably large and he became progressively more obese. In the past, he had never entered into those games with boys that required a display of physical prowess.

Two years before his first examination he began having transient abdominal pains which became progressively worse until just before his first visit when his parents consulted Dr. Alfred Ullman of the surgical staff of the Sinai Hospital, who noted the absence of testes and referred the patient for study.

Physical examination disclosed an obese white male child (Fig. 1). The temperature was 96° F., the pulse rate was 64, respiration 20 and the blood pressure was 110/60. His measurements before treatment compared to normal may be seen from Table I. The normals were borrowed from Engelbach (1932). His obesity was of the pelvic-shoulder-girdle type and his fingers were tapering. His upper central incisors were large and separated from each other by a considerable space. His extremities disclosed a genu valgum, flat arches and tenderness over the tendo achilles. Neurologically, the presence of a cremasteric reflex was

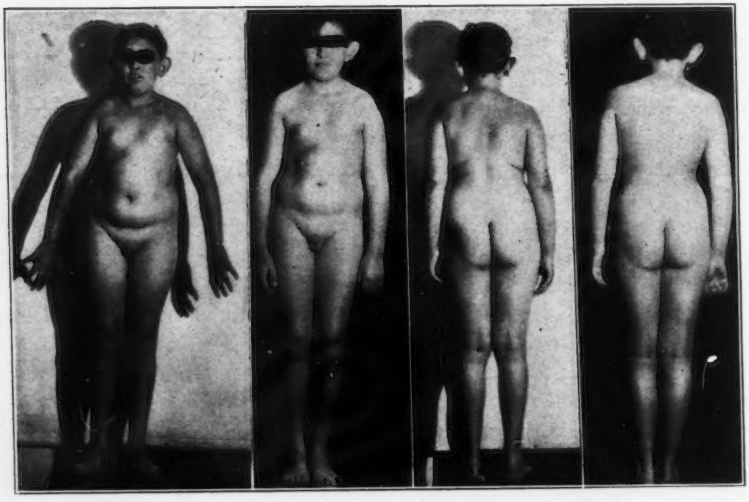

Fig. 1 Fig. 2

Figure 1. Ventral view of patient. Left—Before treatment was begun (6-18-33). Note the typical configuration of dystrophia adiposo genitalis. The penis is small and testes are intra-abdominal. Right—After 5 months' treatment (11-18-33). Obesity noticeably diminished. Body configuration approaching the normal.

Figure 2. Dorsal view of patient. Left—Before treatment (6-18-33). Note girdle adiposity, lateral fat pads from waist to mid-thighs, and marked genu valgum. Right—After 5 months' treatment (11-18-33). Most of the girdle fat has disappeared. The lateral hip region is now flattened; the genu valgum has disappeared.

obviously lacking, due, of course, to the absence of testes from the scrotum. Psychometric study (Binet-Simon) revealed an intelligence quotient of 81.

Examination of his genitalia disclosed an extremely small penis (1½ cm.; Fig. 3) which to a great extent was buried in the fat of the mons pubis. The testes were neither palpable in the scrotum, which was quite flat, nor in the inguinal canals. Pressure over the inguinal canals produced no intra-abdominal pain such as occurs when the testicle is compressed. Roentgenological examination of the skull revealed a normal sella turcica. The basal metabolism was minus 16 per cent. All other laboratory determinations, which included blood studies for cellular and color components, sugar, urea and urea nitrogen, were normal. The Wasserman examination and phenolsulphonphthalein tests were also negative.

In addition to these findings there was marked polydipsia, polyuria, nocturia and enuresis.

TABLE I

SHOWING THE MEASUREMENTS OF HUMAN MALE 10½ YEARS OF AGE BEFORE AND AFTER TREATMENT COMPARED TO THE NORMAL VARIATIONS FOR THAT AGE

	Before Treatment (June 19, 1933)	Normal Variations	After Treatment (November 3, 1933)
Weight (pounds)	99.8	59.9–75.5 relative to optional height 68.6–86.2 relative to actual height	88.8
Height (inches)	56.8	52.4–56.	57.5
Span (inches)	57.	52.5–56.5	57.
Upper Measurement (inches)	28.3	25.7–28.3	28.5
Lower Measurement (inches)	28.5	25.7–28.3	29.
Circumference of Head	21.5	21. (optimal)	21.5
Circumference of Chest	30.	25.7 (optimal)	28.5
Circumference of Abdomen	31.8	23.0 (optimal)	28.5
Circumference of Neck	12.		11.3
Circumference of Hips	33.3		30.3
Circumference of Trochanters	32.5		30.5
Penis (in cm.)	1.5		4.

Because of these findings a clinical diagnosis was made of dystrophia adiposo-genitalis and bilaterally undescended (intra-abdominal) testes.

The patient was treated on an endocrine basis and was given daily intramuscular injections of the water-soluble fraction of pregnancy urine. The dosage, which began with 0.2 cc. (50 rat units), was gradually increased to 1 cc. After six injections it was found that the left testis had entered the inguinal canal and with pressure exerted from above, could be pushed down into the scrotum. When the hand was removed, however, the testicle was spontaneously retracted. At this time the testis was about the size of a small almond (1½ cm. to the feel). The next day the right testis was palpable high in the right canal, and a few hairs appeared over the mons.

Since the testes had successfully passed from the abdomen into the inguinal canals, additional treatment was directed against the other features of the child's disability. This included thyroid extract (gr. ½ t.i.d.) and pituitrin in increasing doses until the intestinal reaction was obtained, after which time the latter drug was slightly diminished.

After three weeks' treatment, thirst and urinary symptoms were abated and for the past two months bed-wetting has not occurred. Injections were continued daily (except Sunday) for two months, after which time they were decreased to three times weekly. After five months' treatment, examination disclosed the measurements as shown in the last column of Table I. From Figs. 1 and 2, it may be noted that at this time there was a moderate reduction of his obesity and that the lateral curvature which extended from his abdomen to his mid-thighs had become flattened. The genu valgum disappeared and the penis had increased from 1.5 cm. (before treatment) to 4 cm. (Fig. 3). His basal metabolic rate had increased to +8 per cent.

In addition, the scrotum became rugose and contained a completely descended testis on the left side and one partially descended on the right. Palpation revealed that these had become larger although measurements were not obtained. Cremasteric reflexes were now present. The prostate gland had become palpable, though small, and a definite increase in pubic hair had become evident. The child has now taken to boys' games, such as football and has expressed a desire to possess a pair of boxing gloves. Re-examination of his mental status (November 13, 1933) revealed an intelligence quotient of 98.

The results obtained in this single case led to several pertinent questions. First, were these results merely coincidental? Was the penis truly enlarged or merely apparently elongated because of the disappearance of pubic fat? Finally, did the pituitary gland which has been held responsible for sex stimulation in the female (Frank, 1931) play a part in the changes noted in this male?

EXPERIMENTAL STUDY

As previously stated, Engle (1932) has already studied the effects of this hormone (unstandardized, however) on rats and monkeys.

For the present purposes four groups of white rats were divided so that each group contained a control and one or two litter mate brothers as test animals. From Table II it may be seen that these were all younger than 40 days, the age at which normal testicular descent occurs in this species. The water soluble fraction of pregnancy urine (the same product as used in the human) was then administered intraperitoneally daily (except Sunday) in a dosage beginning with 0.1 cc. (25 rat units) of the 20 per cent aqueous solution. This amount was increased 0.1 cc. daily up to 0.5 cc., at which level it was maintained.

The number of days of treatment in the different groups (Table II) varied from 13 to 29 days, at the end of which time the animals were weighed, then anesthetized, photographed and sacrificed by bleeding. The latter method of sacrifice has been found advantageous in other studies (Rubinstein, 1932), where comparison of tissues containing minimal amounts of blood was desired. Both testes of each animal were then removed by severing just above the epididymis and weighed together in a weighing bottle. The penis was then dissected out up to the bladder and, after removing the skin, was similarly weighed. Finally, the pituitary gland was removed by the parapharyngeal route (Smith, 1930) and likewise weighed. Although the seminal vesicles were observed and their contents examined, these were not weighed.

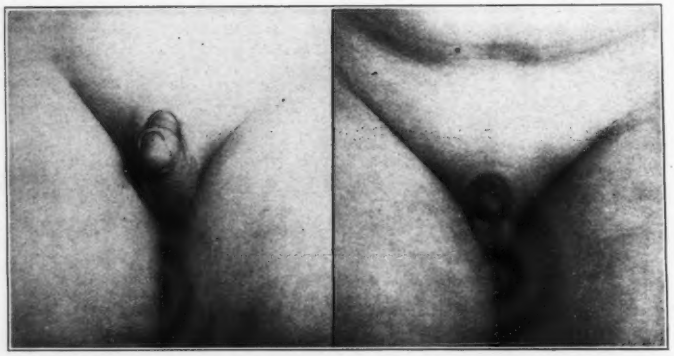

Figure 3. Genitalia of the patient. Right—Before treatment (6-18-33). The penis is small, scrotum flat and testes intra-abdominal. Left—After 5 months' treatment (11-18-33). The penis is 4 cm. long; the scrotum is rugose and contains a completely descended testis on the left and one partially descended on the right. A small growth of pubic hair (invisible on photograph) is also present.

It may be noted from Table II that the extract used failed to increase the body weight of the test animals over that of their controls. This table also discloses the facts that the testes, penes and pituitary glands of the test animals taken as a group were heavier than those of the controls. The seminal vesicles were found to be distended in the test animals but microscopic examination of their contents failed to reveal spermatozoa.

DISCUSSION

Obviously, the results of this experimental study, based as it is upon a relatively small number of animals which when grouped show considerable variation in their ages and bodily measurements, cannot be evaluated by the classical statistical methods. The variation in the animals is so great that calculated probable error would certainly lead to erroneous conclusions. At the same time the series of animals is too small to compute the probable error of each of the four groups separately. In order to overcome

TABLE II

SHOWING INITIAL AND FINAL AGES AND BODY WEIGHTS; TESTICULAR, PENILE AND PITUITARY WEIGHTS FOR ALL ANIMALS

Rat No.	Age in Days				Body Weight gms.				Testicular Weight gms.		Penile Weight gms.		Pituitary Weight gms.	
	Test Animals		Controls		Test Animals		Controls		Test Animals	Controls	Test Animals	Controls	Test Animals	Controls
	Onset	End	Onset	End	Onset	End	Onset	End						
25–2			20	33			22	58		.316		.045		.0011
25–3	20	33			20	50			.336		.075		.0020	
25–4	20	33			19	44			.354		.082		.0020	
26–3			37	62			47	123		1.713		.099		.0098
26–2	37	62			46	121			1.953		.103		.0111	
26–1	37	62			58	132			1.999		.153		.0158	
10–4			14	43			25	115		1.168		.164		.0072
10–1	14	43			25	118			1.180		.235		.0143	
9–2			7	25			18	58		.491		.065		.0110
9–1	7	25			20	61			.775		.113		.0125	
Totals.....					188	526	112	354	6.597	3.689	.761	.373	.0577	.0291
Means.....					31	88	28	89	1.100	.922	.127	.093	.0099	.0073
Deviation from controls.....									+.178		+.034		+.0026	
Gain in body weight (in grams).....					57		61							

this difficulty Table II has been constructed according to litter groups and shows that testicular, penile and pituitary weights were greater, without exception, in all test animals as compared with their controls. Hence, these results are offered as observational data at their face value without statistical consideration. In addition, the specific microscopical changes noted in the testes of the test rats justify the acceptance of these results.

From the results obtained from the human and rat experiments one may safely conclude that testicular descent is definitely influenced by the hormone used. In addition, it is to be noted that testicles so induced to descend are heavier than those of litter mate brothers which had naturally descended (Table II). This increase in size which has been shown by Engle (1932) to be due to an increase in tubular and interstitial substance, has been confirmed in this work.

The absence of spermatozoa in the seminal vesicles is interesting since, although it confirms Engle's (1932) findings, it is at variance with the recent report of Brosius and Schaffer (1933), who claim to have induced spermatogenesis in a human male aged 33 who had become sterile following an attack of mumps at the age of 27. In support of their contribution these workers cite Schockaert's (1931) experiments with the duck in which spermatogenesis was also induced. Without questioning the validity of the observations of Brosius and Schaffer, it is only fair to say that the material used by these investigators (pregnancy urine extract) and by Schockaert (anterior pituitary extract) have not as yet been shown to be identical. Then again, their results were obtained from testicles which had previously produced spermatozoa. Finally, differences in species reaction are undeniable.

The increase in pituitary size is interesting since it is presumptive evidence that the pituitary gland takes part in the process. Of course, histological studies of such glands would add much to the understanding of this process and may be forthcoming in the future.

The behavioral changes on the part of the child, which tended more and more towards the masculine, was undoubtedly influenced by the treatment. That psychic influence was a factor, however, cannot be denied, since as treatment progressed he showed a keen interest in his developing sexuality. Unfortunately, this phase could not be checked by the use of laboratory experiments so that its true evaluation is impossible.

SUMMARY

A human male 10½ years of age with dystrophia adiposo-genitalis and bilaterally (intra-abdominal) undescended testes was treated with the water-soluble fraction of pregnancy urine and the results obtained in this case were checked as far as possible by experimentation with white rats. It was found in the human that the testes descended, the scrotum became enlarged, behavioral changes tended more toward the masculine and improvement in mental status as determined by the Binet-Simon tests oc-

curred. Experimental confirmation on rats disclosed that the six rats treated with the hormone possessed testes, penes and pituitary glands which averaged, respectively, 0.178 gms., 0.034 gms., and 0.0026 gms. heavier than the corresponding organs of their controls. In addition testicular descent in the test rats, regardless of their ages, occurred within 3 to 5 days after the beginning of treatment while in the control animals descent occurred between 40 and 50 days of age. Although the seminal vesicles were enlarged, no spermatozoa were obtainable.

The author appreciates the cooperation of Dr. Morrel of the Squibb Biological Laboratories, who furnished the extract used in this study. Thanks are extended to Dr. Carl L. Davis, head of this laboratory, for his interest and advice and to Dr. L. F. Barker for having read the manuscript.

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THE USE OF PREGNANCY URINE AND PROLAN IN ANIMAL INDUSTRY

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Of all the endocrine preparations stimulating a more rapid growth of flesh and fat in rabbits, only insulin has been hitherto used. The injection of insulin stimulates the assimilation of carbohydrates and through them the formation of fat reserves. However, insulin is a costly preparation and, therefore, not suitable for mass application to animals. The present researches were instituted in a search for cheaper preparations which would produce the same effect. Two substances, prolan (Zondek) and gravidan (sterilized pregnancy urine) were used.

After having independently worked out a method of preparing gravidan I found that 1 cc. of the substance contained 5-8 mouse-units of prolan and 1-3 mouse-units of folliculin. This was true if the urine had been taken within the first three months of pregnancy. Two years of careful study on the subject has led me to the conclusion that gravidan is entirely harmless for animals if administered in moderate dosage.

Gravidan is very different in composition from prolan. Besides the sexual hormones (prolan and ovariin) it contains a number of other hormones, e.g., the hormone of fat metabolism which stimulates a better assimilation of food and the subsequent forming of fat reserves. In 1931 Paal detected the hormone of fat metabolism in the urine of pregnant women. The presence of such hormone in gravidan is particularly valuable for its use in animal industry.

In order to study the toxicity of the preparation I arranged a series of experiments with chronic and acute poisoning of 100 animals (dogs, rabbits and mice). On the basis of these experiments it was found that the toxicity of the preparation was very small. A 20-gram mouse was not affected by an intravenous injection of gravidan but prolan in a considerably lesser dose (0.25-0.50 cc.) caused death. My experiments on the toxicity of gravidan confirmed the data obtained by Zamkov, who had injected gravidan in quantities up to 25 per cent of the weight of the animal without symptoms of poisoning.

The preliminary experiments with rabbits, carried on in the Institute of Experimental Biology, showed that both prolan and gravidan, if administered in small doses stimulated the reproductive system, raised the basal metabolic rate and furthered the assimilation of food. Large doses of the two preparations caused atrophy of the sexual organs, lowered their activity and caused general adiposity through the disturbed fat metabolism.

An experiment was made with 58 adult rabbits (5 females and 53 males) to determine means of stimulating growth of flesh and fat. Of the 58 animals only six were of the meat breed (big Flanders). The other 52 animals were of the fur breed (Russian ermines) about 6-8 months old. All the animals were distributed among four groups. The living conditions for the first group were much better than for the other three groups, as the experiments with this group were carried on in the Institute of Experimental Biology, where the facilities for animal care were better. The food régime for all four groups was the same—50 grams of hay, 50 grams of beet and 50 grams of oats per animal. The studies on each separate group lasted one and a half months. The weight of the animal determined the dosage. The animals were weighed every five days and subcutaneous injections of the preparation were made, while the control animals received subcutaneous injections of the physiological salt solution. The animals of the first group were able to withstand larger doses of gravidan without loss of weight than were the animals of the other three groups. This is presumably due to difference in breed, as the first group consisted of the six rabbits of the meat breed, weighing from 2200 to 3100 grams. The injections were made every other day for one month, and the general observations and weighing continued during a month and a half. (In this first group the experiments were carried out from February 3, till March 18, 1931). In the first group one animal was a control, one was given 0.75 cc. of prolan per kg. of weight every other day, two were given 2-3 cc. gravidan per kg. of weight every other day, and two received 2-3 cc. normal urine per kg. of weight every other day. The findings are shown in Table 1. It will be noted that the rabbits treated with gravidan or prolan showed a considerably greater weight increase, namely, about 3-4 times more than did the controls. Also, the rabbits treated with normal urine showed a weight increase 1½-2 times greater than the controls.

TABLE 1

Preparation	Weight of Animal (grams)	Number of Animals	Dosage Per 1 Kg. (cc.)	Total Amount Admin. (cc.)	Average Weight Increase Per Day (grams)	Total Weight Increase (grams)	Weight Increase (%)
Physiol. salt solution....	3100	1	2.	75.	3.6	162	5.2
Normal urine.....	2700	1	2.	80.	6.6	297	11.0
Normal urine.....	2800	1	3.	160.	5.0	225	8.03
Gravidan.....	2500	1	2.	75.	10.8	486	19.4
Gravidan.....	2950	1	3.	150.	10.8	486	16.4
Prolan.....	2200	1	0.75	18.75	11.2	514	23.3

The studies on the second group were carried out from September 25, till November 10, 1931. Nineteen rabbits were used. Seven control animals received, every 4-5 days, five injections of physiological salt solution (3.1 cc. per animal). Twelve experimental animals received five injections of prolan (3.1 cc., or 25 mouse-units per animal). Injections were made once every five days. The prolan was furnished by the Institute of Endocrinology and was diluted in such proportion that 1 cc. of it contained 8 mouse-units. (One mouse-unit is the minimal quantity which will, 100 hours after injection into an infantile white mouse, produce in it a precocious sexual maturity).

Table 2 shows that the experimental animals in this second group gave a four times greater weight increase than did the controls. The percentage of this increase was 12.1 for the former and 3.2 for the latter.

TABLE 2

Preparation	Weight of Animal (grams)	Number of Animals	Dosage Per 1 Kg. (cc.)	Total Amount Admin. (cc.)	Average Weight Increase Per Day (grams)	Total Weight Increase (grams)	Weight Increase (%)
Physiol. salt solution....	1935	7	3.1	30.5	1.4	66.2	3.21
Prolan.....	1412	12	3.1	23.0	4.0	172.0	12.11

The studies on the third group were carried out from November 2 to December 25, 1931. Six control and twelve experimental animals were used. The control animals received five injections of salt solution (5 cc. per kg. of weight) while the treated animals received 5 cc. of gravidan (five times). During the course of the experiment each experimental animal received, on an average, 41.7 cc. of gravidan. The findings are given in Table 3. It will be noted that the gravidan-treated animals showed an increase in weight almost three times as great as the controls. The increased weight of the former was 9.07 per cent, and that of the latter 3.8 per cent.

TABLE 3

Preparation	Weight of Animal (grams)	Number of Animals	Dosage Per 1 Kg. (cc.)	Total Amount Admin. (cc.)	Average Weight Increase Per Day (grams)	Total Weight Increase (grams)	Weight Increase (%)
Physiol. salt solution....	1696	6	5	36.75	1.5	64.5	3.8
Gravidan.....	1808	12	5	41.7	4.11	176.7	9.07

Experiments on the fourth group were carried out from December 2, 1931, till January 16, 1932. Fifteen animals were used (six control and nine experimental). The dosages and the number of injections duplicate those in the preceding group. The findings are given in Table 4. Here is seen an increase in the weight of all the animals, though, due to a temporary shortage of oats, the weight increase is somewhat lower than in case of the other groups. However, comparing the weight increase in the experimental animals with that of the controls, a definite difference is seen. The former showed an almost five times greater increase than did the latter.

TABLE 4

Preparation	Weight of Animal (grams)	Number of Animals	Dosage Per 1 Kg. (cc.)	Total Amount Admin. (cc.)	Average Weight Increase Per Day (grams)	Total Weight Increase (grams)	Weight Increase (%)
Physiol. salt solution....	1617	6	5	38.26	0.4	18	1.66
Gravidan.....	1599	9	5	43.55	2.0	90	5.62

Of the 38 experimental rabbits used in the course of these experiments only one showed a loss in weight (49 grams), while one kept its weight unchanged. All the other animals showed a weight increase, which was considerably greater than that shown by the control animals.

Two rabbits from the second group and five from the third were killed by stunning and their dressed weight was determined: the internal organs, endocrine glands and pieces of muscle were taken for histological investigation; the flesh was then separated from the bones and the soft flesh passed three times through a meat-grinder; samples of flesh were taken for determination of the water, protein and fat content. The results are given in Table 5. The dressed weight of a control rabbit was 49.9 per cent of the live weight and that of a gravidan-treated animal was 57.2 per cent of the live weight. The interstitial fat constituted 0.9 per cent in the former and 1.8 per cent in the latter. The control animals furnished 85.1 per cent of the soft flesh and 14.9 per cent of bones, whereas, the experimental animals furnished 86.8 per cent of soft flesh and 13.6 per cent of bones. The same picture is seen in rabbits killed after 24 hours' fasting. The dressed weight of a gravidan-treated rabbit was more by 9.2 per cent, the interstitial fat was 2.3 per cent higher and the soft flesh 9.1 per cent higher than in a control. The dressed weight of prolan-treated animals was only 2.04 per cent more than that of the controls and the weight of the soft flesh 3.2 per cent greater. In this instance prolan was less potent than gravidan.

The results in Table 6 show the superior quality of the flesh of the rabbits treated with gravidan, as compared with the control animals. The fat content

of rabbit 32 was 13.0 per cent, and the fat content of a corresponding control was 4.01 per cent. Rabbit 5/50, treated with gravidan, had a fat content of 25.3 per cent, whereas, its control 31/50 had a fat content of only 4.3. The prolan-treated animal gave a fat content of only 1.97 per cent greater than the control.

TABLE 5

Animal No.	Breed	Group	Original Wgt.	Dressed Weight						Separating Flesh From Bones			
						Interstitial Fat		Testes					
			(gms.)	(gms.)	(%)	(gms.)	(%)	(gms.)	(%)	(gms.)	(%)	(gms.)	(%)
110/33	Russian ermine....	Control...	1537	767	49.9	7.	0.91	8	0.5	653	85.1	114	14.9
32	Russian ermine....	Gravidan.	1660	950	57.2	17.	1.8	9	0.5	825	86.8	125	13.2
34	Russian ermine....	Prolan after 24-hour fast.	1590	815	51.3	8.7	1.1	5	0.3	685	84.1	130	16.0
31/50	Russian ermine....	Control after 24-hour fast.	1585	780	49.2	8.	1.0	7	0.4	631	81.0	149	19.1
5/50	Russian ermine....	Gravidan after 24-hour fast.	1837	1072	58.4	37.	3.3	10	0.5	965	90.0	107	10.0

Two possibilities are considered as a cause of the stimulation of growth of fat in the gravidan-treated animals: (1) The presence of the fat metabolism hormone in gravidan stimulates the assimilation of food and the consequent storing in the form of fat; (2) a partial or complete atrophy of the sexual organs, causing the animal to fatten. In the present series of experiments comparatively small amounts of gravidan were injected, which would have produced hypertrophy of the sexual organs, i.e., augmentation in

TABLE 6

Animal No.	Breed	Water	Proteins-Nitrogen	Total Nitrogen	Fat
		(%)	(%)	(%)	(%)
110/33 Control	Russian ermine.....	73.7	20.0	21.6	4.0
31/50 Control	Russian ermine.....	73.0	21.1	21.6	4.3
32 Gravidan	Russian ermine.....	65.5	19.1	21.4	13.0
5/50 Gravidan	Russian ermine.....	56.6	16.0	17.7	25.3
34 Prolan	Russian ermine.....	70.8	19.2	21.5	6.2

volume. It is, therefore, inferred that the stimulation of fat growth was caused by the fat metabolism hormone in the extract. Data obtained by weighing the testicles of both the control and experimental animals corroborate this inference. The testis weight of the experimental animals was greater than that of the controls. The histological investigation of the internal organs, the endocrine glands and muscles of the animals in the second and third group did not show any pathological changes as compared with the control animals.

SUMMARY

A series of experiments to stimulate the growth of flesh and fat in animals were carried out. Fifty-eight adult rabbits were used (20 control and 38 experimental animals). The injection of prolan (13 animals) or gravidan (23 animals) in dosages from 3-5 cc. per kg. body weight produced an increase in flesh and fat in the experimental animals as compared to that in the controls on the same diet. Two animals injected with normal urine also gave a weight increase over the controls. Different breeds of rabbits varied in their toleration for the two substances. The weight of the animal was a necessary consideration in determination of dosage. Prolan was more expensive to prepare, was more toxic when given in larger doses and was less potent in the stimulation of growth of flesh and fat than was gravidan.

IODINE TOLERANCE TEST FOR THYROID INSUFFICIENCY

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Up to the present time the test for determination of the function of the thyroid gland is far from being specific. In order to elaborate a specific test for the function of this gland we based our investigations on iodine metabolism as being closely associated with the function of the gland. Veil and Sturm (1) and other authors have already shown that in hyperthyroidism there exists an increase and in hypothyroidism a decrease of total blood iodine. These observations give a certain basis on which we may obtain a picture of the function of the thyroid gland which may be more exact if we make the determination of blood iodine simultaneously with the examination of the basal metabolic rate. Together with Scheps (2) we have demonstrated that inasmuch as the statement of the increase of these two values proves without doubt the overfunction of the thyroid gland and that the normal blood iodine level (not examined during treatment) excludes the presence of hyperthyroidism, the investigations which concern the detection of thyroid insufficiency are deceiving. Particularly in atypical hypothyroid forms (forme fruste), of which our experiments mainly consist, neither the clinical examination nor the determination of the basal metabolic rate and of the blood iodine give sufficient basis for the detection of these forms. It is known that the clinical picture of atypical hypothyroid forms may be so varied and at the same time so atypical that this fact may easily mislead the clinician. The basal metabolic rate determination, important as it is, may also be misleading. In atypical hypothyroid forms the basal metabolic rate frequently shows values which are near the low normal limit. This masking of the reduction of the basal rate may be noticed most easily in those cases of atypical forms that are followed by disturbances of other glands of internal secretion which are apt even to level the decreased basal metabolism. And if in cases of the above mentioned forms the values of the basal metabolic rate should be even markedly decreased, it is not known whether they may be ascribed, to the thyroid or to other gland insufficiency (hypophysis, adrenals, ovaries, etc.).

However, much as examination of the total blood iodine level has widened our diagnostic methods, there still remain important reservations in the detection of hypothyroidism. Above all, in hypothyroid atypical forms the blood iodine level may be normal as has been convincingly shown in the results obtained by Turner and Matthews (3). In addition there should be mentioned the technical difficulties which arise in the detection of the insignificant decrease of blood iodine in hypothyroidism. If we accept

8γ per cent as the low limit of the normal blood iodine level and, further, if we consider the lowest blood iodine level which could be observed in hypothyroidism to be 3γ per cent (in one case of Veil and Sturm), then it may be seen that in hypothyroidism the blood iodine varies from 3 to 8γ per cent. This observation means that such an insignificant decrease of iodine, e.g., about 6 or 7γ per cent, would be a sufficient basis to ascertain the decrease of blood iodine level, and thus diminution of thyroid function. None of the present micro-methods for the determination of the blood iodine strictly permit the detection of such slight differences.

Our diagnosis of thyroid insufficiency is based, not on the determination of fasting blood iodine, but on a more sensitive test, especially in the experiments on the blood iodine curve observed after administration in the organism of a certain quantity of potassium iodide.

We have shown in our previous investigations (4, 5, 6) that after administration of potassium iodide in the organism, the blood iodine curve remains longer and on a higher level in cases of hypothyroidism as compared with those of normal thyroid function. In hyperthyroidism, however, the blood iodine curve is distinctly opposite, viz., its maintenance on the increased level is much shorter, whereas the total iodine and particularly the organic fraction sinks below the initial level within 24 hours. These results do not agree with those of other investigators (de Quervain and Smith, 7; Sturm, 8; Maurer and Ducrue, 9).

The necessity for two or three blood samples makes this method less adaptable for clinical purposes. It need not necessarily be applied to detect hyperthyroidism because the simultaneous determination alone of fasting blood iodine level and of the basal metabolic rate are sufficient. The examination of the elimination of iodine in urine after administration of potassium iodide is much easier for both the patient and physician. Sturm, de Quervain and Smith, Courth (10) and Schittenhelm and Eisler (11) obtain completely opposite results. From investigations made by Sturm upon dogs deprived of their thyroid glands it is shown that after the administration of potassium iodide by mouth (0.5 gr. KI=370.000γ I) the elimination of iodine in urine does not noticeably differ from the elimination curve of a normal dog. Sturm further reported that the only difference in the normal state is the less uniform elimination of iodine in urine which appears after the administration of iodine. The investigations of Courth, with goats deprived of their thyroid glands, have shown that after administration of potassium iodide (10.000γ I) by mouth the elimination of iodine was more rapid and more augmented than in normal animals. Courth's results agree with those reported by de Quervain and Smith in experiments on humans, viz., in cretins after oral administration of potassium iodide (0.25-1 gr. KI). On the contrary, Schittenhelm and Eisler have shown that after an oral administration of potassium iodide (894γ I) the elimination of iodine in urine in cases of myxedema is not only not increased but even twice diminished. On the basis of these experiments,

carried through in one case only, Schittenhelm and Eisler claim that in thyroid insufficiency iodine metabolism is not disturbed.

In order to obtain a proper clinical picture of the elimination of iodine in urine in thyroid insufficiency, our investigations were carried out on a larger number of patients. In contradistinction to the majority of the authors mentioned previously, we intentionally used small doses of potassium iodide about 1300γ I as KI (which corresponds to the amount of iodine in 2 mg. of thyroxine), for, as stated in a previous publication (4), the percentage of eliminated iodine depends just on the amount of the administered dose. We may further state that small doses which are rather near the physiological amount have an opposite effect as compared with large doses, the content of which amounts to some hundred thousands γ of iodine. We administered the iodine intravenously in order to avoid inaccuracy in the estimation of iodine elimination.

METHODS

All reagents and vessels should be iodine-free, according to Fellenberg (12), and Reith (13).

Dissolve 0.658 g. potassium iodide, dried at a temperature of 110° C., in 500 cc. of iodine-free water. This solution contains 1000γ I in 1 cc. After sterilization keep the solution in 1.3 cc. (1300γ I) amounts in dark phials.

Injection of iodine and its collection in urine. After disinfection of the skin with iodine-free alcohol the content of the phial was injected intravenously and the patient was instructed to drink a glass of water every 1-2 hours for 6 hours. This drinking of water has no influence on the increase of the elimination of iodine (Fellenberg, 12), but facilitates urine output which in hypothyroidism may be frequently insufficient. This dilution of the urine has also the advantage that owing to the diminution of organic matter its incineration is more rapid and may take place at a lower temperature and in consequence the loss of iodine is less marked and the determination made with a higher degree of accuracy. The urine is collected within the first 6 hours after intravenous injection of iodine, for within this period of time the elimination of iodine is chiefly constant and marked, and is the most characteristic for the function of the thyroid gland. As we have shown in our previous publications the elimination of iodine within 24 hours may sometimes show only a slight difference in cases of hypothyroidism and normal thyroid function, but the differences are markedly evident in the first 6 hours after administration. It may be that this is the reason why Sturm, who examined within 24 hours the elimination of iodine in urine in animals deprived of the thyroid gland, instead of within the first 6 hours, found no difference between hypothyroidism and euthyroidism.

Determination. The following modification is added to the method previously described (16). Add to 10-20 cc. urine in a nickel dish 1-1.5 cc. 50% K_2CO_3, evaporate it on a water bath, dry in an electric oven at a temperature of 70-80° C., or carefully over a gas burner, incinerate in an electric oven with the presence of air or oxygen at a temperature of about 350° C. within 10-15 minutes. After cooling the dish, add to the residue a little water, mince the content with an agate pestle and filter with an ordinary blotting filter; the filtrate must be clear or at the most slightly yellow. Incinerate the filter with its content in the nickel dish in an electric oven within 10 minutes at a temperature of 350° C. After complete incineration the residue of the filterate must be of a pure white color. This modification markedly simplifies and hastens the determination.

The rest of the procedure is made according to the method previously published (16).

Our investigations were carried out in 55 cases of different diseases with normal or disturbed function of the thyroid gland. They were divided into the following groups:

I. Euthyroid cases with normal blood iodine level and with normal or decreased basal metabolic rate.

II. Hypothyroid cases with decreased or normal blood iodine level and with decreased basal metabolic rate.

III. Hyperthyroid cases with increased blood iodine level and increased basal metabolic rate.

IV. Cases of non-toxic goiter with normal blood iodine level and with normal or decreased basal metabolic rate.

TABLE 1

EUTHYROID CASES WITH NORMAL BLOOD IODINE AND WITH NORMAL BASAL METABOLIC RATE

No.	Sex	Age	Diagnosis	Elimination of Iodine in Urine in γ After 1300 γ Intravenously	Percentage of Iodine Eliminated in Urine	Remarks
(a) Euthyroidism with normal blood iodine level (8 to 18γ%) and normal basal metabolic rate (−10 to +10%):						
1	♀	30	Neurosis vegetativa.....	248	18.	
2	♀	10	Diabetes insipidus.....	232	17.	
3	♂	37	Ischialgia.....	198	14.5	
4	♂	21	Nihil..	248	17.6	
5	♀	39	Ca. uteri not operable.....	274	20.	
6	♀	47	Myomata uteri.....	222	16.	
7	♀	30	Obesitas.....	1 7	12.	
8	♂	63	Neurasthenia.....	258	19.8	
9	♂	38	Tbc. genu.....	187	12.8	
10	♀	41	Ca. uteri operable.....	275	20.	
11	♀	30	Obliteratio tub. ovari.....	280	20.5	
(b) Euthyroidism with decreased basal metabolic rate (−12 to −32%) and with normal blood iodine level (from 9 to 18γ%):						
12	♂	15	Retarded development of growth. Pituitary insufficiency.....	178	13.	
13	♂	28	Neurosis vegetativa.....	210	15.	
14	♀	37	Neurosis vegetati a.....	253	19.7	
15	♀	54	Ins. ovar. arthritis chr.....	184	13.4	
16	♀	36	Ins. plurigl. Addison (?)....	212	15.8	
17	♀	29	Neurosis cordis. tachycardia	253	19.1	
18	♀	18	Dystr. adip. gen. tumor hypoph.....	153	11.7	
19	♀	33	Psychosis. Mania depressiva	259	19.1	

In this group are collected 19 subjects who clinically show no disturbances in the function of the thyroid gland. In these patients the percentage of eliminated iodine in urine within 6 hours after intravenous injection of 1300γ I varied between 11.7 and 20.5 per cent. We have not noted significant differences in iodine elimination in cases of normal and decreased basal metabolic rate.

TABLE 2

HYPOTHYROID SUBJECTS WITH DECREASED OR NORMAL BLOOD IODINE LEVEL AND WITH DECREASED BASAL METABOLIC RATE

No.	Sex	Age	Diagnosis	Elimination of Iodine in Urine in γ After 1300 γ Intravenously	Percentage of Iodine Eliminated in Urine	Remarks
			(a) Hypothyroid cases with decreased basal metabolic rate (from −34 to −59%) and with decreased blood iodine level (from 4 to 6γ%):			
20	♀	62	Myxoedema	353	27.	
21	♂	43	Myxoedema	328	24.4	
22	♀	35	Myxoedema	532	40.1	
23	♀	52	Myxoedema	394	27.	
24	♂	62	Myxoedema	328	25.	
25	♂	4	Kretinismus	389	30.	The decrease of basal metabolism could not be strictly stated by lack of proper breathing.
			(b) Hypothyroid subjects with decreased basal metabolic rate (from −22 to −38%) and with iodine level between 7 and 9γ%:			
26	♂	33	Forme fruste. Eczema gen.	420	32.3	
27	♀	56	Forme fruste. Anthropathy gen. endocrin	427	32.	
28	♀	53	Forme fruste. Anaemia gravis	360	27.	
29	♀	56	Forme fruste. Arthropathy gen. endocrin	302	23.2	
30	♂	33	Forme fruste. Anaemia	426	32.7	
31	♂	42	Forme fruste. Obesity	412	31.	
32	♀	48	Forme fruste. Climacterium	334	25.7	
33	♀	28	Forme fruste. Peribronchitis	333	25.6	
34	♀	49	Forme fruste. Struma resid. p. strumect	379	29.2	
35	♂	42	Forme fruste. Neurosis cordis	316	23.	
36	♀	33	Ins. plurigl. Amenorrh	333	26.	Basal metab. rate −10%, iodine in blood 9γ%.

In all 17 patients with the clinical picture of hypothyroidism, the elimination of iodine within 6 hours after intravenous injection of 1300γ I is markedly increased and varies from 23 to 40 per cent. The increase of the elimination of iodine does not always correspond with the reduction of the basal metabolic rate. We cannot find any remarkable differences existing between the elimination of iodine in urine in cases of hypothyroid typical and atypical forms. Special attention is to be given to case 36, the clinical form of which represents a pluriglandular disease with normal blood iodine and normal basal metabolic rate. Despite this masking of the reduction of the basal metabolic rate which may also be the result of levelling influence of other glands, we can establish on the basis of this positive iodine tolerance test hypothyroid insufficiency.

TABLE 3

HYPERTHYROID CASES WITH INCREASED BLOOD IODINE LEVEL AND WITH INCREASED BASAL METABOLIC RATE

No.	Sex	Age	Diagnosis	Elimination of Iodine in Urine in γ After 1300 γ Intravenously	Percentage of Iodine Eliminated in Urine	Remarks
(a) Severe hyperthyroidism with basal metabloic rate from +40 to +100% and with iodine in blood from 25 to 64γ%:						
37	♀	22	Exophthalmic goiter.....	34	0.8	
38	♀	38	Exophthalmic goiter.....	108	7.2	The patient has taken over a long period 200 mg. diiodotyrosine per day. The taking was finished three weeks before.
39	♂	28	Exophthalmic goiter.....	343	24.	
40	♂	44	Exophthalmic goiter.....	402	29.	The patient interrupted before few weeks the treatment with Lugol's solution.
(b) Mild hyperthyroidism with basal metabolic rate from +18 to +50% and with increased blood iodine level from 20 to 36γ%:						
41	♀	51	Exophthalmic goiter.....	292	21	
42	♀	36	Exophthalmic goiter.....	249	18	
43	♀	29	Exophthalmic goiter.....	190	14	
44	♂	30	Exophthalmic goiter.....	351	24	Iodine medication (Lugol's solution), the patient has finished before few weeks.
45	♂	10	Exophthalmic goiter.....	196	14	
46	♀	40	Hyperthyreosis and scleroderma.....	252	19	

In this group we collected 10 cases showing clinical symptoms of hyperthyroidism. In the subjects with more severe symptoms the percentage of iodine eliminated in urine within 6 hours decreased by 0.8 to 7.2 per cent when no iodine was applied in any form. In mild cases in which there was no treatment with iodine the percentage of eliminated iodine was normal (from 14 to 21 per cent). However, either in more or in less severe cases in which there was iodine treatment the percentage of eliminated iodine in urine may show an increase. Sturm (13) also noted the fact that after the first administration of iodine in cases of exophthalmic goiter the percentage of eliminated iodine in urine is lower as compared with euthyroidism and increases after frequent administration of iodine. This may be taken as evidence that the hyperthyroid organism becomes sensitive after frequent administration of iodine and reacts by an increased elimination of iodine as compared with euthyroidism.

In conclusion it will be noted that in hyperthyroid subjects without previous administration of iodine the percentage of the eliminated iodine is either decreased or normal, in subjects treated with iodine, however, the elimination of iodine in urine within 6 hours may be increased.

TABLE 4

NON-TOXIC GOITER WITH NORMAL OR DECREASED BASAL METABOLIC RATE AND WITH NORMAL BLOOD IODINE LEVEL

No.	Sex	Age	Diagnosis	Elimination of Iodine in Urine in γ After 1300 γ Intravenously	Percentage of Iodine Eliminated in Urine	Remarks
(a) Non-toxic goiter with normal blood iodine level from 8 to 14γ% and with normal basal metabolic rate from −10 to +10%:						
47	♂	17	Struma simpl. diff.....	146	11.2	
48	♀	24	Struma simpl. diff.....	170	12.4	
49	♀	45	Struma simpl. diff.....	100	7.1	
50	♂	50	Struma simpl diff.....	95	7.	
51	♀	56	Struma simpl. nodosa.....	52	4.	
52	♀	48	Struma resid. post. strumect.	185	13.6	
(b) Non-toxic goiter with normal blood iodine level from 8.5 to 10γ% and with decreased basal metabolic rate from −12 to −27%:						
53	♀	20	Struma simpl. diff.....	45	3.4	
54	♂	26	Struma simpl. diff.....	77	5.5	
55	♂	25	Struma simpl. nodosa.....	246	18.6	

In all 9 subjects of non-toxic goiter the percentage of eliminated iodine within 6 hours is either decreased from 3.4 to 11 per cent just as in some hyperthyroid subjects, or normal from 12.4 to 18.6 per cent. In not one case, even in those with a markedly reduced basal metabolic rate, was the elimination of iodine increased. We have noted no relationship between the form and the size of non-toxic goiter and the character of the elimination of iodine after administration of iodine.

On the basis of investigations in 55 cases we may state that the elimination of iodine in urine shows, after the intravenous administration of 1300γ I (potassium iodide), a striking difference in hypothyroid cases as compared with cases of euthyroidism, hyperthyroidism and non-toxic goiter. Namely, in hypothyroidism the iodine tolerance test is always positive, i.e., the elimination of iodine in urine within 6 hours shows a striking increase and amounts to 23-40 per cent of injected iodine, whereas in all other cases with normal or pathological function of the thyroid gland our test is constantly negative, i.e., the percentage of eliminated iodine is either normal as in euthyroidism or in hyperthyroidism or in some cases of non-toxic goiter, or decreased as in some cases of hyperthyroidism or of non-toxic goiter. Our test may also be positive in some hyperthyroid cases in which iodine was previously applied.

This fact does not diminish the test value for detecting thyroid gland insufficiency, for the increase of the basal metabolic rate and eventually

also of blood iodine will always permit, even in doubtful clinical cases the distinction between hypothyroidism and hyperthyroidism.

As an explanation of the difference which exists between the behavior of iodine in urine after intravenous administration of iodine in hypothyroidism and euthyroidism, we refer to our investigations (4, 5, 6) in which we undertook the simultaneous determination of blood and urine iodine curve after intravenous administration of iodine. As a result of this investigation we were able to state that the increased elimination of iodine in urine in the first 6 hours is parallel to the continued and high maintenance of the increased blood iodine which does not reach the initial limit even after 24 hours. This we cannot confirm in euthyroidism in which the increased level after 6 hours is to be found almost at the initial point and in hyperthyroidism it sinks even markedly lower. These experiments show that in hypothyroidism the tissues, and particularly the thyroid gland, do not fix the iodine of the blood as much as in euthyroidism and hyperthyroidism. That the disappearance of intravenously injected iodine, more rapidly in cases of euthyroidism and hyperthyroidism than in hypothyroidism, is the consequence of its more marked absorption by the organs and not of the more rapid and higher elimination of iodine in the urine, is proven by the fact that the elimination of iodine in urine is at the same time less pronounced in euthyroidism and in hyperthyroidism than in hypothyroidism. We agree with Fukushima (15) that the hypofunctional thyroid gland, and particularly the hypothyroid organism, has markedly lost the power for fixing and retaining iodine, yet we are opposed to the opinion of Maurer and Ducrue, to wit: that these processes are independent of the function of the thyroid gland.

This diminished power of fixing the iodine injected into a hypothyroid organism explains why in hypothyroidism our test is positive, i.e., why the elimination of iodine in urine after its administration is markedly more increased than in euthyroidism.

We mentioned previously that the greatest difficulties in the diagnosis exist in atypical hypothyroid forms, in which it cannot be supported either by the clinical picture or by the determination of blood iodine and basal metabolic rate, which are frequently normal or slightly decreased; (these variations may be also the result of faulty technic in the determination of iodine or of the basal metabolic rate).

We believe that for a diagnosis in these atypical forms our test is of particular value, because of its constant and positive results.

It will also be noted that our negative test in subjects with a decreased basal metabolic rate permits the exclusion of thyroid insufficiency and causes us to look elsewhere for the cause of this decrease.

Finally we desire to call attention to the fact that after administration of iodine the determination of iodine in urine is much more easy to make as compared with the determination in blood, because of the higher concentration of iodine in urine than in blood.

SUMMARY

1. An iodine tolerance test is described that has been found to be highly characteristic of hypothyroid insufficiency.

2. The percentage of eliminated iodine in urine within 6 hours after intravenous injection of 1300γ I as KI showed in hypothyroidism (17 cases) a constant and marked increase and amounted to 23-40 per cent, in euthyroidism (19 cases) to 12-20.5 per cent, in hyperthyroidism (10 cases) and in non-toxic goiter (9 cases) it was either decreased (as much as 0.8 per cent) or normal. The increased elimination was also noted in three patients with hyperthyroidism to whom iodine had been previously administered. This fact does not diminish the value of our test, for not only the clinical picture but the simultaneous determination of the basal metabolic rate and the fasting blood iodine enables us, in a definite way, to differentiate between these two diseases and to detect the presence of hypothyroidism.

3. Our test is of special value for the determination of atypical hypothyroid forms, for which the clinical picture, the determination of fasting blood iodine, or the examination of the basal metabolic rate do not give sufficient grounds for the diagnosis of hypothyroidism.

4. In all subjects with decreased basal metabolic rate the negative results of our test exclude hypothyroid insufficiency and cause us to search elsewhere for the cause of the decrease.

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DIGESTIVE SYMPTOMS IN CHRONIC SUPRARENAL INSUFFICIENCY (ADDISON'S DISEASE)

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We have studied the digestive disturbances in a series of 160 certain cases of Addison's disease. The frequency of these troubles is extraordinary, since normal findings were obtained in only 12 per cent of the cases.

The following table shows a summary of the symptoms presented:*

	Cases	*Percentage*
Intense hunger	3	1.8
Inappetence	142	88.7
Dyspepsia	61	38.0
Nausea and sickness	39	24.3
Gastric ulcer	3	1.8
Diarrhea	45	28.0
Constipation	35	21.8
Pseudo-peritonitis	11	6.8
Hiccough	43	26.8
No digestive symptom	19	11.9

We propose to make a brief analysis of these symptoms:

Intense Hunger. In some of the classical works on Addison's disease, mention is made of intense, even painful, hunger: Kussmaul (1), Auerbeck (2), Bittorff (3). Three of our patients mentioned this symptom spontaneously, either as a permanent symptom or as a post-prandial crisis. In our three cases, this hunger occurred at the beginning of the disease, disappeared later and in two cases changed to anorexia.

We have sometimes imagined that this symptom could be related to the hypoglycemia which is frequent in Addison's disease. We have recently shown that the disturbance of the regulating mechanism of the carbohydrates in this disease is sometimes shown by a relative post-prandial hyperinsulinism (due to lack of compensatory secretion of adrenalin) which is clinically manifested by the usual hypoglycemic symptoms, among which is hunger. However, this hypothesis is opposed to the fact that the symptom disappears in the later phases of the disease, at which time the hypoglycemic tendency is most marked.

*In the earlier clinical data of our files we note the lack of information of certain categories which we now investigate systematically. For the present purposes we consider that the former cases were negative, if there is no mention of digestive symptoms, although there might have been symptoms of a veiled character. In any case, although this does not reflect the exact position, there is little distortion, because the great majority of our cases are relatively recent.

The painful type of hunger at times recalls the typical form of duodenal ulcer, which would cause one to think such an ulcer might exist, since certain authorities, as we shall show later, consider suprarenal insufficiency to be an important pathogenic factor of gastro-duodenal ulcer. However, there were no symptoms of ulcer in any of our three cases.

Inappetence. This, as the table shows, is the most frequent symptom. It almost invariably appears early, sometimes years before the clinical evidence of typical Addisonian symptoms. It is interesting to note how rapidly this symptom is relieved by cortical opotherapy. In our opinion, this symptom is most intensive when the patient suffers from scarcity or lack of hydrochloric acid. In certain cases inappetency is so marked that the mere sight of food provokes defensive nausea, and seriously hinders feeding the patient.

Dyspepsia. There were 61 cases in which our patients complained of sundry gastric disturbances which, for lack of uniformity, we have classed as "dyspepsia." In some cases, when there is hyperchlorhydria or organic hyperacidity, these disturbances take on the hyperchlorhydric type (immediate or tardy post-prandial acidity and saliva); in other cases, those which are more numerous, there are vague symptoms of heaviness, gastric plenitude, meteorism, somnolence, etc.

These symptoms are frequently accompanied by an epigastric pain which is fixed or has various irradiations.

Nausea and Sickness. Nausea and sickness (39 cases), appear especially in the patients with hypochlorhydria, ascertained or clinically induced Vomiting may be immediate or tardy, of varied aspect, and generally very bilious. Such patients are always difficult to treat and sometimes the vomiting is uncontrollable.

At times, vomiting precedes the final stages of the disease, especially the digestive type of coma (pseudo-peritonitis). This intensive vomiting of Addisonian patients has been compared to that of certain pregnant women, especially those who are highly pigmented, and it will be remembered that some authorities claim that this vomiting is of a hypo-suprarenal nature. We cannot enter into this discussion here, but we can say, as data supporting that hypothesis, that adrenaline (although not confirmed by all authors) has a beneficial effect on that type of vomiting, and a still better effect is obtained with modern cortical extracts.

Gastric Ulcer. Auerbeck (2) mentioned that in some of his Addisonian patients there was an epigastric pain and other discomforts which "resemble those of gastric ulcer." Friedman (4) and others state that they have produced the ulcer experimentally by extirpating the suprarenal glands of animals. But the most profound study of the relationship between Addison's disease and gastric ulcer has been carried out by Hermando (5). According to this author, the cause of the frequent co-existence of both

processes would be: (a) the lymphatic constitution, which is typical of Addisonian patients and which in addition is favorable to the growth of the ulcer; (b) possibly hyperchlorhydria, which is not uncommon in the early phases of suprarenal insufficiency; (c) also the vagotonic constitution of Addisonian patients and (d) finally, these causes may be seconded by an infection which destroys the suprarenal glands and may also react on the gastric mucous membrane.

In our patients, however, we have seen only three certain cases of ulcer. In post-mortem examinations of Addisonian patients (25 cases) we have never found old or recent erosions, of an ulcerous type, on the mucous membrane. Only one of the subjects showed scars which made us suspect a small old ulcer on the minor curvature. Schmidt (6) also states that in his patients (25 certain Addisonians), he found no gastric ulcer. Diehl (7) observed only one Addisonian patient with an ulcerous condition and he states that the ulcer was not a consequence of the suprarenal insufficiency, but rather that both the gastric and the suprarenal lesions were a consequence of chronic gastro-enteritic, mainly enteritic, lesions.

Both of these authors, and also Friedman (3) and Crile (8) consider that the ulcer is a consequence of a combined disturbance of the suprarenal and the thyroid glands, but this is merely a hypothesis with no important clinical or experimental foundation.

All this is related to the state of gastric chymism in Addison's disease. Grawitz (9) was the first to note the frequency of achylia in this disease, and this has latterly been confirmed by almost all authorities. Several state that this achylia is tardy, and that in the early stages of the suprarenal process there is probably a normal chymism or hyperchlorhydria [Bauer (8), Lucien and Parisot (11), Zondek (12), Rowntree (13), Boenheim (14), Friedenwald and Morrison (15)]. But Hernando reminds us that there are Addisonian patients with hypochlorhydria from the beginning, and cases in which the hyperchlorhydria is maintained until the end. Other authors, Ehrman and Dinkin (16) and Cohoe (17), have found a normal chymism in their Addisonian patients. However, none of these authors, except for isolated cases, give exact figures for the chymism.

We have carried out this investigation on relatively few of our Addisonian patients, because the technique is very trying, especially for subjects who were constantly undergoing analysis of greater importance. However, we investigated the chymism of 13 certain cases of Addison's disease (6 after the breakfast of Ewald-Boas and a partial chymism of the other 7). The results obtained are shown in the table on next page.

This shows that in more than half the cases, viz., 7, there was a decrease or a suppression of the hydrochloric secretion. In two cases only was there a marked hyperchlorhydria, in one case slight hyperchlorhydria, and in three cases the chymism was normal.

In two of the cases of hypochlorhydria (IX and X) the total acidity remained within normal limits.

No.	Observation	Sex	Age	Prognosis	Total Acidity	Free HCl	Digestive Diagnosis
I	16858	F	35	Slight.....	3.60	3.06	Hyperchlorhydria ulcer
II	46–15	F	47	Slight.....	2.52	2.00	Hyperchlorhydria ulcer
III	14813	M	34	Grave.....	1.80	1.25	Hyperchlorhydria (slight)
IV	46–8	F	25	Slight.....	1.60	1.095	Normal
V	46–7	F	20	Slight.....	1.31	1.02	Normal
VI	10003	F	40	Slight.....	1.24	1.09	Normal
VII	46–8	F	56	Grave.....	1.02	0.73	Hypochlorhydria
VIII	10355	M	32	Initial.....	0.91	0.62	Hypochlorhydria
IX	10750	M	24	Slight.....	1.61	0.55	Hypochlorhydria
X	44–9	M	21	Grave.....	1.53	0.29	Hypochlorhydria
XI	44–9	M	28	Grave.....	0.0	0.0	Apepsia
XII	10735	F	26	Very grave.....	0.0	0.0	Apepsia
XIII	10047	M	20	Grave.....	0.0	0.0	Apepsia

In general, hypochlorhydria or anachlorhydria occurred in patients with advanced and grave forms of the disease. On the other hand, the mild cases generally showed normal secretion or hyperchlorhydria. The exceptions are in Case VIII, initial and slight with hypochlorhydria, and in Case III, grave with normal acidity. We do not insist on this detail, as the prognosis for these patients is extremely treacherous, since some have a scanty symptomatology but die rapidly, whereas others show very marked symptoms, yet keep well for long periods, even several years.

Hernando (5) and other authors suggest that one of the causes of these disturbances of the gastric chymism may be the neuro-vegetative alteration of Addisonian patients, principally the excessive vagal tone, caused by the decrease of the sympathetic tone, which is inherent on the decrease or disappearance of the physiological stimulus, viz., adrenaline. However, this assumed vagotonia of Addisonian patients, although frequently mentioned in books, does not exactly correspond to reality as has been shown by Vazquez Velasco (18). After studying the state of excitability and the state of the vegetative tone in a series of 16 certain cases of Addison's disease, with a very accurate technique (that of Danielopulo, modified by Vazquez), he came to the conclusion that there is a decrease of the vegetative tone, as a general rule, and also a general decrease of the vegetative excitability, more notable with respect to the sympathetic than the vagus, although there is no real vagotonia.

In addition, we have studied the gastric chymism and the neuro-vegetative state of six of our Addisonian patients with the following results:

No.	Observation	Vagal Tone	Vagal Excitability	Sympathetic Tone	Sympathetic Excitability	
II	46–15	Low (12)	High (38)	Low (104)	Low (30)	Hyperchlorhydria
IV	46–8	Low (20)	High (26)	Low (88)	Low (26)	Normal
V	46–7	Normal (44)	High (52)	Normal (120)	Normal (44)	Normal
VIII	10355	Low (16)	Low (14)	Normal (124)	High (52)	Hypochlorhydria
X	44–9	High (60)	High (108)	High (144)	Normal (42)	Hypochlorhydria
XIII	10047	Low (28)	High (62)	Normal (124)	High (62)	Apepsia

That is to say, for instance, that in a case of hyperchlorhydria (II) the vagal tone was low and the vagal excitability was slightly increased. In a

case of hypochlorhydria (X) the vagal tone and excitability were both high. In a case of achylia (XIII) the vagal tone was low and the excitability was high. In brief, there is evident an absence of a definite connection between the state of the gastric secretion and the formula of the neuro-vegetative equilibrium. This leads one to suppose that the mechanism of these gastric disturbances has no bearing on the vegetative system.

Diarrhea. Various authors mention that diarrhea is very frequent in these patients. We have observed it in 28 per cent of our cases. It generally appears in conjunction with suspicious gastric disturbances which point to hypochlorhydria, and presents all the characteristics of gastrogenous diarrhea. The analysis of faeces by Hernando (5) confirm that there is nothing specific in this symptom. In some cases, the diarrhea does not appear until the final, precomatose period. In children suffering from Addison's disease, we have not observed the very intensive diarrhea mentioned by Finkelstein (19).

Constipation. We have noted the existence of constipation, generally not excessive, in 35 cases (21.8%). Almost without exception it was necessary to ask the patient about this symptom, as they attached no importance to it.

Sometimes constipation alternates with diarrhea. Friedenwald and Morrison assert that it is frequent for the disease to begin with constipation and end with diarrhea (15), but this process is not always observed. An interesting problem, in connection with the above, is whether certain chronic gastro-intestinal lesions, of a specific etiology or not, can also give rise to suprarenal insufficiency with an incomplete syndrome (Addisonism) or with the complete syndrome of Addison's disease. Long ago it was suggested that certain symptoms which are not uncommon in gastropathy of long standing might have a suprarenal origin, such as asthenia, a dark earthy pigmentation of the face, and sometimes of mucous membranes, hypotension, etc. Returning to this question recently, Diehl (7) asserts that there is an "Addisonism in chronic gastro-enteritis." He bases his thesis on four cases, whose diagnosis as suprarenal insufficiency is not convincing. None of the the subjects had a post-mortem examination; two were old dysenteric patients; one had a digestive disturbance, probably of saturnine origin and one, mentioned previously, had a duodenal ulcer. We have recently seen a case which coincides with the two dysenteric patients of this author.

No. 10727. A married woman, 48 years old, had been suffering for 14 years with cholic pains, blood-stained mucous diarrhea and tenesmus. She was the mother of six children and had the menopouse at the age of 37. She reported periods of constipation. She had a pycnic constitution and was obese. The heart and lungs was normal. The arterial tension was 120-80. The urine was normal. Tests for syphilis were negative. In the faeces, cysts of amoeba dysenterica, amoeba coli and other unclassified cyts were found. The patient experienced considerable improvement with estovarsol treatment. Two months later she returned, saying that she had been intoxicated with some decayed food. The weight was reduced by 8 kg. There was marked asthenia, absolute gastric intolerance, and attacks of hiccough. The pulse rate was 120, and the arterial

tension was imperceptible. She showed diffuse pigmentation typical of Addison's disease, with a discrete pigmented spot on the upper gum above one of the middle incisors (the favorite place, according to our experience, for the beginning of bucal pigmentation). Our diagnosis was acute suprarenal insufficiency, probably connected with dysenteric infection. We have had no further news of the patient.

Pseudo-peritonitis. Among the digestive symptomatology of suprarenal insufficiency, we attribute a great importance to the pseudo-peritonitis syndrome. Although frequently mentioned by authorities, in the clinics it is sometimes overlooked, and it is not uncommon to find the diagnosis has been made for a real peritonitis, and the patient advised to undergo an operation, as in the following case:

A married woman, 46 years old, with no children, had always been weak and asthenic. Six years before she began to suffer from gastric disturbances, which were diagnosed by several specialists as hyperchlorhydria, after investigation of the gastric chymism. In spite of treatment, she had periods of considerable discomfort, which recurred constantly. Two years ago there was noticed a slight melanoderma, and the chronic asthenia became more marked. These symptoms were considered trivial until their Addisonian nature was diagnosed and an adequate treatment prescribed (cortical extracts were not yet available). The patient improved for several months. Then, after a long journey, fatigue produced a digestive syndrome which was, to all appearance, peritonitic. The abdomen was hard and meteorised and there were diffuse abdominal pains. The pulse was almost imperceptible. The extremities were cold, and there was nausea and uncontrollable vomiting, hiccoughing, hippocratic facies and hypothermia. In view of a previous diagnosis of ulcer it was thought that there might be a gastric perforation, and it might be advisable to operate at once. The surgeon, with a wide clinical experience, made the correct diagnosis of a pseudo-peritonitic Addisonian accident and, conseqently, refused to operate. His diagnosis was confirmed and an adequate treatment was prescribed. The patient improved for a time, the peritoneal symptomatology disappeared, but she died a few weeks later from suprarenal insufficiency. As the patient lived in the country, where there were no facilities for investigation, no analysis was possible during the final period. Addison's clinical tableau was very pronounced and offered no doubt when I saw the patient.

This syndrome was observed in 11 (6.8%) of our patients, all except two, in whom the pseudo-peritonitic symptoms were temporary, being in the pre-mortal period. Even those two died shortly afterwards, although with different symptomatology. One of these two cases was the one mentioned as not having received cortical hormone. The other one received this treatment. Other authors also confirm the efficacy of the cortical hormone when injected in sufficient doses, in the treatment of this accident of suprarenal insufficiency, but after a certain time, the patients relapse and die, in spite of the treatment, either with a pseudo-peritonitic syndrome, or with either of the other syndromes which bring about the final phase of this disease.

Investigations carried out by one of us (20) show that this pseudo-peritonitic syndrome is an acidosic accident. We have demonstrated the importance in this final period of Addison's disease, of the appearance of acidosic phenomena, due to the exhaustion of the hepatic glycogen, and the consequent inability of the organism to metabolize the proteins and fats (acidosis by hypoglycogenesis) (21).

Hiccough. Although hiccough is really a respiratory and not a digestive symptom, we include it in this survey on account of its clinical and pathogenic connection with the phenomena we have been examining.

From our earliest experience with Addison's disease, we were surprised to note how often hiccough appears as a symptom. Patients refer, sometimes spontaneously, that after meals, or generally with no apparent bearing on food, they had attacks of hiccoughing which may have been slight, or were sometimes prolonged and tenacious. We were surprised to find that pathologists had paid no attention to this symptom and therefore have investigated systematically all our Addisonian patients, with the result that we have observed the symptom in 43 cases (26.8% of our series). It must be borne in mind, in order to estimate the real frequency of this phenomenon, that patients usually consider hiccough to be a trivial complaint, unless the attacks are very violent, and they do not mention it unless specially questioned on this point.

We have mentioned above that none of the classical descriptions of Addison's disease refer to this symptom. As exceptions, Bittorf (3) mentions an Addisonian patient with violent hiccough, and in a recent monograph Levy Simpson (22) refers to two cases in which cortical opotherapy caused the symptom to disappear rapidly.

The pathogeny of Addisonian hiccough is, to our mind, quite clear. It its doubtless a phenomenon which is related to the acidosis mentioned above. Annes Dias (23) calls attention to the significance of hiccough as a symptom of acidosic states, and we ourselves have confirmed this to such an extent that whenever we have a patient with hiccough, we systematically investigate the reaction of his blood.

Of course, the hiccough appears, as stated above, together with the pseudo-peritonitis already described, and is a clear contribution to its clinical characterization, with no other digestive or acidosic symptomatology. However, it always reveals a deviation of the acido-basic equilibrium towards acidosis, in our opinion, and therefore is a delicate indication that the disease is nearing its final period. In the prognosis of the disease we wish to call attention to the significance of Addisonian hiccough. Its mere appearance should be a sufficient warning that the patient is in danger of a serious crisis, and therefore the necessary therapeutic precautions should be adopted.

Absence of Digestive Symptoms. In 19 of this series of 160 Addisonian patients (11.9%), the investigation of the digestive apparatus gave negative findings in spite of the fact that in some of them the suprarenal insufficiency was very intense.

Digestive symptoms are therefore frequent, but not constant in this disease.

SUMMARY

We have investigated the frequency of pathological manifestations of the digestive apparatus in 160 certain cases of Addison's disease.

The most frequent symptom in inappetence: it is almost constant. Next in frequency come divers dyspepsias, diarrhea, nauseas and vomiting, and constipation. Other gastric or intestinal symptoms are less frequent.

Special interest has been taken in the study of the gastric chymism. Half the cases considered show hypochlorhydria or anachlorhydria. This gastric state frequently, but not always, coincides with the most serious perioids of the disease. We have found no connection between the type of the disturbance of the gastric chymism and the neuro-vegetative alterations.

In our experience, it is not frequent for gastric ulcer to coincide with Addison's disease.

The study of the pseudo-peritonitic accidents is of special interest for the diagnosis as they are an indication of acidosic states which are generally pre-mortal.

A very high percentage of Addisonian patients have attacks of hiccough, either in conjunction with the pseudo-peritonitic syndrome, or alone. In both cases they indicate the final acidosic state, and consequently point to an unfavorable prognosis.

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THE FAT TOLERANCE TEST IN PITUITARY DISEASE

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The importance of the pituitary gland in fat metabolism is generally recognized. Opinions as to the relative significance of the anterior and the posterior lobes in regard to fat metabolism are still controversial; for, until recently, the posterior lobe was credited with the more momentous function in the regulation of fat deposit and oxidation. The recent work of Anselmino and Hoffman (1), however, has focused attention upon a special fat metabolism hormone that can be extracted from the anterior lobe and distinguished from its other active principles. If this hormone is injected into animals, it elicits an increase in the acetone bodies of the blood (acetone, acetoacetic acid and betahydroxybutyric acid). The hormone is discharged into the circulation after the ingestion of a fatty meal, and gives rise to the same significant results as are obtained by the injection of the pituitary extract.

The presence of the hormone in the circulation can be demonstrated by the withdrawal of blood after the fat meal and the injection of the serum into another animal. The rise of the blood acetones of the latter is like that obtained by the injection of pituitary extracts.

It would seem that the reaction of the anterior lobe to the intake of fat is comparable to that of the pancreatic islands to the ingestion of carbohydrates. Both glands discharge their specific hormone into the circulation intermittently upon stimulation of fat and carbohydrate intake, respectively. The interesting discovery by Anselmino and Hoffman has been confirmed by Magistris, Boenheim and Heiman, and Eitel, et al. Raab could not confirm these findings, but the evidence he contributes is too scanty to carry particular weight.

Stimulated by the publication of Anselmino and Hoffman, we studied the effect of pituitary extracts on the blood acetones. While the German authors used animals in their experiments, we preferred to repeat their work on humans. The extracts were prepared according to Anselmino and Hoffman's directions, and one to two cubic centimeters was injected subcutaneously into our patients. Blood samples were withdrawn before the injection and two other samples were taken one and two hours after the injection. A quantitative determination of acetone bodies on all three samples was made according to the method of Behre and Benedict.

After the precipitation of the blood proteins by the Folin-Wu method, 2 to 3 drops of a 1.1 concentrated sulphuric acid are added to 50 cc. of the

blood filtrate. Twenty-five cc. are collected by slow distillation and used for the estimation of the preformed acetone and the acetone from the diacetic acid. The residue is brought to a boil and 30 cc. of a 1.1 concentrated sulphuric acid and 20 cc. of 0.2 per cent potassium bichromate solution are added gradually through a dropping funnel, while a slow distillation goes on. After 10 minutes 50 cc. of a 0.2 per cent potassium bichromate are added slowly and the same is repeated again in ten minutes. The distillation is to occupy at least 30 minutes and a volume of 100 cc. is collected. This portion contains the acetone derived from the beta hydroxybutyric acid.

The quantitative determination is made by the colorimetric method and checked by the iodometric method. For the colorimetric method a standard stock solution containing 0.01 mg. acetone per cc. is made up. From this stock solution into test tubes are placed 0.5 cc. up to 5 cc. and water is added in each instance to make the volume 5 cc. Thus a range of known standards is made (from 0.005 to 0.05 mg. per cc.). Five cc. of the first distillate is poured into another test tube and 5 cc. of each of the known standards are taken; and all are uniformly treated. To each tube 5 cc. of a 32 per cent sodium hydroxide solution is added and then followed by 10 drops of salicylic aldehyde. All tubes are immersed in a bath of boiling water for 5 minutes. They are then removed and allowed to cool. The color comparison is made by using the known standard of such a concentration that the unknown solution gives a reading between 11 and 19 mm. with the standard solution set at 15 mm. The following formula is then used to calculate the acetone in milligrams per 100 cc. of blood. X/R x P/S x T/5 x 100, where X is the reading of the standard solution; R is the reading of the unknown solution; P is the number of mg. of acetone in the standard; S is the number of cc. of blood used; T is the number of cc. of distillate.

The iodometric determination is made as follows: To 10 cc. of distillate 10 cc. of N/10 iodine is added. The solution is alkalinized and allowed to stand for 5 minutes. Then it is acidified. N/10 sodium thiosulphate is added until the iodine is used up, with starch as an indicator. The difference in cubic centimeters between the amounts of the iodine and the thiosulphate used represents the amount of the iodine taken up in its reaction with acetone. One cc. of iodine is equivalent to 0.967 mg. acetone.

We observed considerable individual variations in the acetone content of human blood, the values obtained ranging from 0.1 to 4.0 mg. per cent. In each individual, however, the acetone content in the fasting stage showed very little variation if testing was repeated during a period of two hours. A series of 10 cases was used for these control experiments.

In another series of 30 cases we determined the acetone content of the blood before and after the injection of the pituitary extract, and obtained a rise in acetone bodies. In some cases, however, but little changes were noted. In view of the fact that these patients had been picked at random

and we had no means to analyze their condition, no conclusions could be drawn, nor any attempt made to explain the lack of uniformity in their response to the pituitary extract. Seventy-five per cent of the tested patients showed the expected rise of the acetone bodies and substantiated the presence of the fat metabolism hormone of Anselmino and Hoffman. (Fig. 1.)

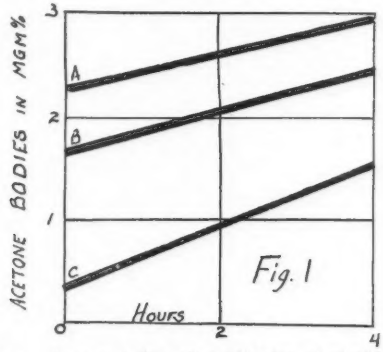

Figure 1. Acetone bodies after injection of pituitary extract.

It seemed that the production of such a hormone by the pituitary gland would lend itself to diagnostic purposes, if the observation of Anselmino and Hoffman is correct, that this hormone is actually discharged into the blood stream upon the ingestion of fat. We felt that a different response should obtain in case of pituitary disease with disturbed function of the gland. With the purpose in mind to utilize the physiological reaction of the pituitary gland to the ingestion of fat the following procedure was devised.

Fasting patients were given a test breakfast consisting of 4 ounces of heavy sweet cream diluted with the same amount of milk, one ounce of butter with two slices of toast. A sample of blood was withdrawn before the meal, and two others were taken one and two hours after the breakfast was consumed. Quantitative determinations of the acetone bodies were made on all three samples.

CHART I

CHANGES IN THE ACETONE CONTENT OF THE BLOOD

Type of Case	Rises	Drops	No Change	Total
Thyroid	13	..	..	13
Thyropituitary	13	5	..	18
Pituitary	8	36	13	57
Treated Pituitary	8	..	..	8
Gonadal	4	1	1	6
Adrenal	2	..	..	2
Non-Endocrine	5	..	..	5
Total	53	42	14	109

Our studies were carried out on 109 patients including varied types of endocrinopathies from our endocrine clinics along with several normal controls. Chart I shows the distribution of our material grouped according to the clinical diagnosis. The patients classified as suffering from pituitary disease included two cases of Simmond's cachexia, two cases of pituitary dwarfism, two cases of acromegaly, while the other patients showed obesity with typical fat distribution, mostly combined with menstrual disorders. We distinguished as thyropituitary cases a group of patients that showed developmental evidence of preadolescent thyroid failure or other clinical signs indicating that the thyroid factor was not merely a secondary incident in the course of the pituitary deficiency.

According to this chart about one-half of the patients showed a rise in the acetone content as the expected physiological reaction, while 56 cases showed no rise or an actual drop of the acetone bodies. These abnormal reactions were observed only in cases which were clinically assigned to the pituitary or thyropituitary group, except in two cases of primary gonadal insufficiency. Our material indicates that a drop or the absence of a rise in the blood acetone after a fat meal occurs practically only in pituitary disease and seems to be pathognomonic for such a condition. A rise of the acetone bodies after a fat meal, however, does not rule out pituitary disease, as about two-thirds of our thyropituitary and one-seventh of our pituitary cases for a total of 28 per cent of the total pituitary material showed the physiological rise. Those pituitary patients who had been given prolonged organo-therapy prior to the test, showed a rise suggestive of improved pituitary function subsequent to treatment.

In order to study the effect of treatment we examined the fat tolerance in four patients before and after organo-therapy was given. As shown by Chart II the blood acetone level generally decreases upon treatment. The

CHART II

THE ACETONE CONTENT OF THE BLOOD IN THE COURSE OF TREATMENT

		Before	After
SA	Fasting	1.01	0.97
	1 H. P. C.	0.77	0.19
	2 H. P. C.	0.68	0.61
B	Fasting	0.97	0.87
	1 H. P. C.	0.39	0.19
	2 H. P. C.	0.19	0.96
W	Fasting	1.35	0.37
	1 H. P. C.	0.39	0.98
	2 H. P. C.	0.19	0.90
SI	Fasting	4.51	1.12
	1 H. P. C.	5.10	1.00
	2 H. P. C.	4.73	1.65

reaction to the test also suggests a tendency to normalization, except for the first case, in which the drop after the test meal still persisted. In the second case there is still a drop at one hour after the test meal but the rise above normal follows within two hours. The third and fourth patient

showed perfectly normal reactions upon re-examination. These four re-examined cases, together with eight other treated cases, confirm our impression that the abnormal response to the fat tolerance test gives way to a normal reaction upon continued specific organo-therapy.

Our findings as presented by Chart I indicate that what we propose to call the fat tolerance test is a valuable aid in the diagnosis of pituitary disease. No rise of the acetone bodies in the blood after the test meal constitutes evidence of pituitary deficiency; whereas a rise does not rule out pituitary disease, although it does not favor such a diagnosis. Observations indicating discharge of the fat metabolism hormone from the pituitary in spite of other convincing evidence of pituitary failure are not inconsistent with our general concept of endocrine physiology and pathology.

It is well established that the diversified functions of the pituitary are dissociated; that is, one function may be deficient in one direction, while other activities are normally, or even excessively, attended to. Thus, it is not unusual to find signs of pituitary failure, such as genital hypoplasia and obesity combined with accentuated growth, or stunted growth with normal sexual development and nutrition. It is perfectly consistent with these observations that a patient may suffer from a pituitary insufficiency and show clinical signs thereof, without any decrease in the production of the fat metabolism hormone. This is not a common occurrence in our experience but its possibility must be emphasized in order to properly evaluate the results obtained with the fat tolerance test.

The 42 cases in which a drop of the blood acetone was obtained were subjected to further analysis by the introduction of two other tests, the diagnostic significance of which seems to be established. We have reference to the determination of the specific dynamic action according to the method described by Goldzieher and Gordon, and to the estimation of uric acid in the blood. The average of the specific dynamic action of these 42 cases (Chart III) was only 6.3, which is well under the average of 16.3 in the control cases of Goldzieher and Gordon. Although the occurrence of values above 10 is 29 per cent, that is substantially more than that in the pituitary group examined by Goldzieher and Gordon, it still strikingly differs from the 79 per cent of their control group.

It is important to point out that 12 cases, 28.5 per cent of the whole group, had a specific dynamic action of 0. This is also less than the 36.5 per cent of the paper quoted, but yet quite a contrast to the 1½ per cent of its control group. Determination of uric acid in our 42 cases (Chart III) showed an average of 3.9 milligram per cent as compared with 2.7 in an extensive series of unselected control cases. The figure is even higher than the average obtained in all our other non-pituitary endocrinopathies (3.6 per cent) and favorably compares with the figure of 4.1 mg. per cent which we obtained as an average for a series of well over 200 cases of hypopituitarism. More than one-half of the 42 cases showed uric acid values above 4 mg. per cent.

CHART III

RELATION OF DROP IN BLOOD ACETONE TO

Specific Dynamic Action			Uric Acid		
Cases	Per Cent	S. D. A.	Cases	Per Cent	U. A. in Mg. %
12	28.6	0	3	7.1	Below 3
18	42.8	Below 10	16	36.7	From 3 to 4
12	28.6	Above 10	23	56.2	Above 4
Total 42	Total 100.	Average 6.33	Average.....	.....	3.91 mg. %

Determination of the specific dynamic action and the blood uric acid gives results that are in keeping with those of the fat tolerance test. Occasional low values for uric acid in 7 per cent of the cases and somewhat more frequent high normal values of the specific dynamic action in 28½ per cent of the cases does not detract from the significant coincidence of these three abnormal reactions in patients clinically diagnosed as hypopituitaries.

It is easily possible that an even more consistent overlapping of the results of these diagnostic procedures could be obtained with technical improvements of the fat tolerance test. With this in mind we studied on a smaller series the different fractions of the acetone bodies and particularly the betaoxybutyric acid. Chart IV shows results in 17 cases, of which

CHART IV

Patient	Diagnosis	Total Acetone Bodies			Oxy-Butyric Acid		
		Fasting	1 H. P. C.	2 H. P. C.	Fasting	1 H. P. C.	2 H. P. C.
Silv.....	Pit.....	0.42	0.37	0.19	0.32	0.32	0.15
Fe.....	Pit.....	1.64	0.97	1.06	1.16	0.48	0.58
Ka.....	Pit.....	0.10	0.14	0.10	0.10	0.	0.10
Mu.....	Pit.....	2.90	3.00	2.88	0.78	1.35	0.84
Cy.....	Pit.....	1.95	1.46	2.29	0.84	0.44	0.79
Gr.....	Pit.....	1.23	0.62	1.15	0.48	0.14	0.36
Sch.....	Pit.....	0.29	0.29	0.29	0.10	0.10	0.10
	Average.....	1.22	0.95	1.14	0.54	0.40	0.42
Ser.....	Thy.-Pi	1.94	3.50	2.27	0.20	1.42	1.17
Ru.....	Pit.....	1.47	4.06	2.21	0.49	1.06	1.45
Gra.....	Thy.-Pit.....	2.13	1.81	3.97	0.82	0.75	1.81
Sau.....	Thy.-Pit.....	0.37	0.62	1.12	0.03	0.12	0.30
Sh.....	Thy.-Pit.....	0.87	1.64	2.61	0.48	1.35	0.58
For.....	Thy.-Pit.....	1.26	1.45	1.45	0.59	0.87	0.77
Mag.....	Acromeg.....	0.63	0.77	0.63	0.39	0.39	0.10
Mus.....	Thyr.....	0.29	0.39	0.58	0.10	0.19	0.10
Si.....	Pit.....	4.51	5.10	4.73	1.61	2.08	2.46
Si.....	Treated.....	1.12	1.00	1.65	0.56	0.46	0.93
	Average.....	1.46	2.03	2.12	0.53	0.87	0.97

7 showed a drop in total acetone content, while 10 showed a rise. In the former group only clinically pituitary cases were found, while the latter consists of thyropituitary and thyroid cases in addition to two cases of pituitary insufficiency and one case of acromegaly. Comparing the averages of the total acetone and oxybutyric acid, we noted satisfactory agreement. It would seem, however, that the rise of the oxybutyric acid is slightly more accentuated. Paradoxical reactions or discrepancies are also

less frequent and less marked in the oxybutyric group, which would seem to offer some advantages for diagnostic purposes.

The nature of the fat metabolism hormone has given rise to controversy. Eitel, Lohn and Loeser maintain in their recent preliminary report that the fat metabolism hormone is identical with the thyrotrope principle of the anterior lobe. These authors failed to obtain the rise in acetone bodies if the pituitary extract was injected into thyroidectomized animals. If this observation would be correct, the rise in acetone bodies would have to be interpreted as a response to the thyroid hormone discharged upon stimulation by the thyrotrope principle of the pituitary. It would also indicate that a fat tolerance test along the lines suggested in this paper would not be applicable for the differential diagnosis of pituitary and thyroid failure, or at least would be more likely to identify the latter.

The experiments quoted, however, are contradicted by the observation of Anselmino and Hoffman, who showed that a rise of blood acetone, obtained after the injection of thyroxin, differs considerably from that elicited by the pituitary extract. Fig. 2 taken from the paper quoted

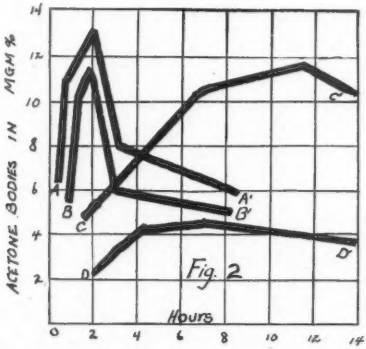

Figure 2. After injection of pituitary extract. A-A', Total Acetone. B-B' Oxybutyric Acid. After injection of thyroxin. C-C', Total Acetone. D-D' Oxybutyric Acid.

demonstrates that the response to thyroxin sets in much later, at a time when the effects of the fat metabolism hormone are already wearing off. The thyroxin curve reaches its peak at twelve hours while the acetone bodies return to their original level eight hours after administration of the pituitary extract. The curve also shows a difference in the relation of the oxybutyric acid to the total acetone. After the injection of the pituitary extract the rise of the oxybutyric acid is parallel with that of the aceone bodies, reaches its peak simultaneously, and forms altogether the bulk of the increase. The rise of acetone bodies after thyroxin injection is attributable only to a minor degree to an increase in oxybutyric acid. The latter reaches its peak earlier and declines already before the eighth hour.

Anselmino and Hoffman's work has been corroborated by Magistris, who noticed that the fat metabolism hormone was thermolabile, whereas the

thermostability of the thyrotrope hormone is generally recognized. Magistris also confirms the observation that repeated administration of the fat metabolism hormone does not increase the basal metabolic rate, in contradistinction to the effect of the thyrotrope hormone. Magistris mentions, moreover, that he had injected fat metabolism hormone to some thyroidectomized animals and observed the rise in acetone bodies just the same.

Our own clinical observations bear out the experimental findings of Anselmino and Hoffman and Magistris. They are hardly compatible with the assumption that fat metabolism and thyrotrope hormones are identical.

SUMMARY

1. The presence of a fat metabolism hormone of the anterior lobe of the pituitary, which causes a rise of the acetone bodies of the blood, is confirmed.

2. A similar rise of blood acetone after intake of a fat meal seems to denote the physiological discharge of the fat metabolism hormone.

3. A fat tolerance test was devised to demonstrate the functional status of the anterior lobe of the pituitary.

4. The test meal consists of four ounces of heavy sweet cream, four ounces of milk, one ounce of butter and two slices of toast.

5. Examination of 109 cases after a test meal showed absence of the physiological rise of blood acetone bodies in 56 cases which consisted almost exclusively of those of pituitary deficiency.

6. A rise was obtained in the normal controls, in all other endocrinopathies, and also in some hypopituitary patients.

7. The physiological reaction was obtained in those hypopituitary patients who had been under specific organo-therapy over a prolonged period of time.

8. Analysis of the 42 cases in which the blood acetone content dropped after a test fat meal showed a low specific dynamic action averaging 6.3 per cent; the blood uric acid of these cases averaged 3.9 mg. per cent.

9. The consistent combination of a low specific dynamic action, high uric acid and increased fat tolerance appears to characterize pituitary insufficiency.

10. Preliminary studies suggest that the determination of oxybutyric acid instead of the total acetone content is likely to improve the results of the fat tolerance test.

11. The relation of the fat metabolism hormone to the thyrotrope hormone is discussed, and the distinct identity of the two principles emphasized.

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LUTEINIZATION OF THE OVARY OF THE MONKEY BY MEANS OF COMBINED USE OF ANTERIOR PITUITARY EXTRACT AND AN EXTRACT OF PREGNANCY URINE*

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In previous communications evidence was presented which indicates that the gonad-stimulating, anterior-pituitary-like substance from urine of human pregnancy does not act as a follicle activator in the rhesus monkey (Engle, 1933, 1934).

In those instances where massive doses of the pregnancy urine factor were administered intravenously, no increase in oestrin production resulted. The changes were in general regressive in nature, but in many of the larger and medium sized follicles luteoid changes occurred, particularly in the theca interna. Most frequently the granulosa was entirely cytolized in the atretic process set up by the action of the active principle of human pregnancy urine. In cases where this cytolysis did not occur, some of the cells of the granulosa underwent hypertrophy, forming sporadic clumps of typical lutein cells. While a smaller quantity of this substance given intravenously over a longer period would perhaps form typical corpora lutea, from certain practical considerations it was desired to maintain a certain amount of oestrin production until functional corpora lutea were produced. For this reason it was desirable to unite the follicle-stimulating fraction of the anterior pituitary gland with the extract from urine of human pregnancy.

The present report presents the protocols of nine monkeys in which this method was used and a brief discussion of the morphological response.†

My 120—a 3000 gm. prepubertal animal. The right ovary was removed. It measured 7.8 x 5.0 x 3.9 mm. and weighed 128 mg. The left ovary was smaller in mass, 7.3 x 6.1 mm. It had large follicles only. Five cc. of anterior pituitary extract was given twice daily for 7 days (35 cc.=18 gm. dried sheep AP). On the 5th day of treatment there was excellent reddening and rugae forming. On the 8th day APy+PU (PU. 1:60, about 30 RU/cc.) were mixed in syringe and given intravenously for 13 days. The proportionate dosage of AP was lowered gradually, and the PU was raised. Due to venous occlusion the treatments of the last three days were given part intravenously and part subcutaneously. The total dosage of the combined fractions was 27.7 gm. dried sheep AP and 2.5 liters whole pregnancy urine. The left ovary measured 8.7 x 7.1 x 6.0 and weighed 200 mg.

This treatment resulted in complete luteinization, a "mulberry ovary" with a certain degree of functional capacity (Fig. 1).

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†The dried sheep anterior pituitary and the Antuitrin S used in these experiments were furnished through the cooperation of Dr. O. P. Kamm of Parke, Davis and Company. Follutein was supplied by E. R. Squibb and Sons, through the courtesy of Dr. J. A. Morrell.

My 122—weighed 3200 gm. 11/30/32. The right ovary was removed. It measured 6.7 x 4.6 x 3.5 and weighed 67.5 mg. The left ovary at this time (6.9 x 3.8 x 3.1 mm.) appeared larger than the right. On Dec. 6 the color was neutral and there had been no bleeding since operation. Two cc. APy + 2 cc. Ant. S (100 U/cc.) were mixed in syringe and given twice daily subcutaneously for 7 days. On the 6th day there was slight purpling and oedema of the sex skin. The color advanced slightly but not so much as in My 120 with the same APy. On the 8th day the same mixture was given intravenously twice daily for two days. On the 10th day the proportions were changed to 1 cc. APy, 3 cc. Ant. S and was given once daily intravenously for 14 days. On the 5th day of this last treatment all color had gone; on the 8th day the sex skin was ashy grey. On the 7th day there was blood in the vaginal lavage and on the 8th day there was external flow. Oestrin was given on the third day to save uterus. Bleeding stopped after one day. The total treatment was the mixture of APy and Ant. S given subcutaneously for 8 days and intravenously for 16 days. The left ovary measured 6.7 x 4.0 x 2.9 mm. and weighed 57.6 mg.

The control (Rt.) ovary had many good growing follicles. In the experimental ovary were many atretic follicles with granulosa greatly reduced or absent. There were hundreds of primordial follicles with cyto-

Figure 1. Photomicrograph of section of left ovary of a young monkey, No. 120, showing the extent of luteinization as a result of combined treatment of AP and PU.

lized ova and sclerosed thecae. Seven corpora lutea were present, having developed from medium sized follicles. These consisted of discrete bodies packed with cords of lutein cells and no central lumen and others with a periphery of lutein tissue and a central cavity into which the spindle cells had migrated (Fig. 2).

My 166—a 4450 gm. multiparous animal had bled from Oct. 2 to Oct. 6. On Oct 12 there was pudendal swelling and redness. The right ovary was removed and measured 5.8 x 4.3 x 3.4 mm. and weighed 50.9 mg. The left ovary was larger, measuring 6.3 x 3.9 x 3.5 mm. It was left intact. There were no corpora lutea. Two cc. of APy was given subcutaneously the day after operation and for six days. On the 6th day there was swelling and color. On the 7th day, 2 cc. APy (60 RU) and 1 cc. Follutein, 1250 RU., a pregnancy urine derivative, were mixed in syringe and given intravenously for five days. The left ovary was removed the day after the last treatment. It measured 7.3 x 4.6 x 3.8 mm. and weighed 94.5 mg. Haemorrhagic follicles were visible. There was uterine bleeding on the day of the operation—six days after the first injection of Follutein and seven days after unilateral ovariectomy.

The ovary contained one very large follicle, and several smaller ones, in which haemorrhage had occurred. This follicle was denuded of granulosa, and its fluid and blood filled antrum was bounded by the thickened theca interna. There were also five or six large corpora lutea.

Transition stages between these two types were seen in small, unchanged follicles, in corpora with a central blood filled lumen, and small corpora with typical luteal cells composing the entire body.

My 167—4300 gm. The sex skin was faded. The right ovary was removed and measured 7.8 x 5.7 x 4.4 mm. It weighed 103.7 mg. The left ovary was larger, measuring 8.8 x 5.4 x 3.9 mm. There were no corpora lutea and the ovary was left intact. Bleeding after ovariectomy was checked by oestrin (Amniotin, 100 U. daily). The sex skin was neutral. Two cc. APy was given subcutaneously for seven days. By the 7th day there was noted excellent color and swelling. Two cc. APy + 1 cc. Follutein (a pregnancy urine product, 1250 U/cc.) was given intravenously for five days. Color was gone. The left ovary was

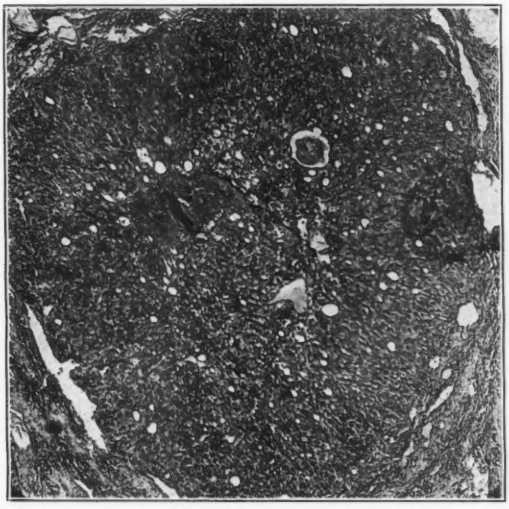

Figure 2. Section of left ovary of monkey No. 122, showing a typical corpus luteum with retained ovum.

removed. It measured 9.7 x 7.8 x 5.5 mm. and weighed 249.7 mg. About 20 haemorrhagic follicles were seen in the ovary. There was no uterine bleeding until after removal of the second ovary.

There was considerable lutein change in the theca of the follicles of this ovary, but there were no solid corpora. One interpretation of the results is that the AP treatment forced the follicles into the cystic condition seen in Fig. 3, and that while the addition of the PU factor arrested this process, it did not cause luteinization. In the monkeys studied, no instance of luteinization of a cystic follicle has been observed, although production of oestrin promptly ceases.

My 118—3950 gm. The sex skin was slightly colored. The ovary was small on palpation. Two cc. AP aqueous pyridine extract (50 units) was given daily by the subcutaneous method. After seven days pachydermatosis with a deep red color was noted. The AP extract was discontinued. An alcohol-ether laboratory

preparation of concentrated pregnancy urine (3 cc., about 60 units) was given intravenously for nine days. The color had disappeared by the 7th to 9th day. There were no red blood cells in the vaginal lavage. The left ovary was removed. It measured 9.2 x 5.7 x 4.5 mm. and weighed 151 mg.

The ovary contained two haemorrhagic follicles without granulosa but with a thickened theca, and many medium and large follicles with normal ova and granulosa, all with thickened theca. There was a mass of sclerosed, solid atretic follicles without ova. Treatment with PU was continued intravenously, 5 cc. (125 units) on seven additional days. External bleeding occurred on day 5 after ovariectomy. The right ovary was removed. It measured 7.1 x 5.4 x 4.4 mm. and weighed 135 mg. There were very few normal follicles with granulosa and ova; even the smallest follicles without antra were sclerosed. There was little or no lutein change.

Fig. 3

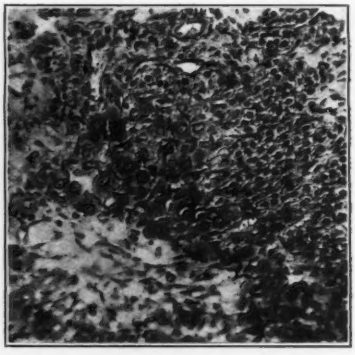

Fig. 4

Figure 3. Section of left ovary of monkey No. 167. In this case, the ovary had been forced into a cystic condition with the extract of anterior pituitary. The addition of the AP-like factor of pregnancy urine merely caused a moderate thecal thickening and a large number of haemorrhagic follicles, without any characteristic luteinization.

Figure 4. Section showing transition of follicle to a luteoid condition in monkey No. 133, left ovary. Even though the granulosa cells have not greatly enlarged they show the characteristic corded or columnar arrangement of the developing corpus luteum.

My 141—3850 gm. AP was given subcutaneously for 10 days. An excellent red coloring and swelling was noted progressing from the 5th to the 10th day. On the 11th day 2 cc. PU (Benzoic acid method, about 100 units daily) was added to 1 cc. AP (30 units) and administered intravenously for eight days. The left ovary measured 9.4 x 6.6 x 2.9 mm. and weighed 133 mg., while the right measured 8.8 x 5.7 x 3.5 mm. and weighed 135 mg. at the beginning of the experiment.

The right ovary had many growing follicles, no C.L., and atresia not greater than usual. The left ovary after treatment had a few unchanged follicles, and scores of involuted follicles, much as though PU had been given alone. Among the atretic and hyalinized follicles were very few with true lutein cells. This was the least successful of the attempts at luteinization.

My 133 was an infantile animal weighing 2000 gm. The right ovary was removed and measured 6.8 x 5.2 x 3.7 mm. It weighed 91.4 mg. The left ovary, measuring 7.8 x 4.0 x 3.7 mm., was left intact. Two cc. aqueous pyridine extract (30 cc.=10 gm. dried sheep AP) was given subcutaneously for seven days. On

the 5th day there was noted slight anal reddening which was further increased by the 7th day and for five additional days. On the 8th day, 2 cc. Antuitrin S (100 U/cc.) was added to the AP and given subcutaneously for four days. On the 12th day the AP was reduced by half and the Antuitrin S increased by 1 cc. (now AP 1 cc., Ant. S. 3 cc.—300 units). On the 12th day the color had definitely faded. Treatment continued to the 19th day. The total was 7 days AP extract and 20 days of AP + PU subcutaneously. The left ovary measured 8.3 x5.8 x 5.0 mm. and weighed 128.6 mg. The uterus had been examined and threaded on the 12th day of the combined treatment.

There were a very few small follicles with normal granulosa and antrum, and a very large number of sclerosed atretic follicles. There were many transitional stages tending toward corpora lutea (Fig. 4). These were small and medium sized, none as large as the corpora in Fig. 1, but each had distinct luteal cells, often with the ovum enclosed. These transitional bodies will be discussed in greater detail subsequently.

My 135 was an infantile animal weighing 3000 gm. The left ovary was removed. It measured 8.7 x 4.8 x 3.1 mm. and weighed 95.1 mg. The right ovary measured 9.0 x 4.8 x 2.6. The sex skin was neutral. APy in 2 cc. dosages was given subcutaneously for 11 days. The first response of the sex skin was noted on the 8th day and progressed to the 11th day. This animal was treated at the same time as My 133 and with the identical extract but with much less results. On the 12th day 2 cc. Antuitrin S (100 U/cc.) was added to the AP and given subcutaneously for 18 days. Uterine bleeding occurred on the 8th day and intermittently for eight days. The right ovary was removed the day after the last injection and measured 8.0 x 5.4 x 3.3 mm. It weighed 89.5 mg.

The control (left) ovary had many large growing follicles, with a minimum of atretic involution. The experimental ovary had several apparently normal follicles, no completely formed C.L. and rare atretic follicles in luteoid transition. The majority appeared to be passing directly from the atretic follicle with cytolized granulosa to the sclerosed body.

It was reported previously that an extract of the water soluble fraction of the anterior pituitary subcutaneously administered did not cause luteinization of the ovarian follicle of the monkey. Several attempts with intravenous injections of this water soluble fraction have not given unequivocal results, although Hisaw, et al. (1932), have reported such a change. A typical instance is shown by the protocol.

My 124 weighed 4800 gm. Menstrual bleeding occurred 12/8 to 12/12/32. Oestral skin was well developed by 12/27. The left ovary was removed. One large follicle and one old corpus luteum were noted. The ovary measured 8.3 x 5.7 x 5.1 mm. and weighed 141.1 mg. On the day of the operation and the day following, 2 cc. AP (60 units) was given subcutaneously. On the 3rd, 4th, 5th, 6th and 7th days 3 cc. (90 MU) was given intravenously. The right ovary was removed on the 8th day. It measured 6.0 x 4.6 x 3.4 mm. and weighed 56.9 mg. Color and pachydermatosis increased progressively throughout.

The experimental ovary had numerous follicles in active proliferation, all about the same size. There was little atresia and no haemorrhagic follicles. There was no change toward luteinization in any of the large follicles. Some of the smaller ones were in a process of atretic involution. In this adult animal taken in the follicular phase of the cycle, no important changes toward luteinization had occurred after intravenous injection of a moderate dosage of aqueous extract of the anterior pituitary gland.

DISCUSSION

Complete luteinization of almost all of the ovarian follicles of the monkey has been obtained in some cases by means of preliminary treatment with the folicle-stimulating, aqueous fraction of the anterior pituitary, which has been followed by the intravenous injection of both the extract of the gland and extracts derived from human pregnancy urine.

The data regarding the action of the anterior pituitary extract, demonstrating it to be a follicular activator in the monkey, need not be discussed here (Hisaw, et al., 1931, 1932; Engle, 1933). Similarly, the pregnancy urine factor has not caused follicle activation in any of the wide range of dosages, methods of administration or length of therapy (Engle, 1934). Several different commercial preparations from pregnancy urine have given uniformly negative results.

When given subcutaneously over varying periods of time the ovarian changes are invariably regressive in nature. The first overt symptom is the prompt cessation of oestrin production.

In adult monkeys, where relatively high dosages were given intravenously, this checking of oestrin production occurred uniformly, but in that series, the majority of ovaries showed tendencies of thecal change toward luteinization, although complete and characteristic corpora lutea were not demonstrated.

It was assumed that, as in many other mammals, the granulosa contributes to the formation of definitive corpora lutea in the monkey. If the pregnancy urine factor could not cause proliferation and maturation of the granulosa, it was desirable to ascertain the action of a known follicle activator preceding, and then combined with the pregnancy urine factor.

The most convincing results were obtained in immature animals. The must successful was in My 120, where subcutaneous administration of the anterior pituitary factor, resulting in follicular activity and sex skin response, was followed by combined intravenous injection of a progressively decreasing amount of the glandular extract with a progressively increasing amount of the pregnancy urine fraction.

In other cases, 133, 135, in which the entire treatment was given subcutaneously, the lutein response was slight, small bodies being present, transitional stages of atretic involution being the most prominent.

One case of failure of luteinization is important. Monkey 167, an adult animal, was pretreated with AP extract with a spectacular response of the sex skin. In this animal the subsequent combined treatment with the two extracts did not result in the formation of a single complete corpus luteum. The interpretation offered after examination of the treated ovary is that the AP factor had precipitately forced the follicles into a condition of cystic degeneration. In this animal also the addition of the urinary principle was accompanied by a rapid loss of conditioning of the sex skin. Due to the advanced stage of cystic degeneration, in which the granulosa

was greatly decreased, no distinctive luteal bodies were found, the entire change being in the theca.

It is evidently essential that the follicles be in an active proliferative phase before the action of the pregnancy urine factor can be manifested in other than a regressive phase. Monkey 122 received both extracts from the first injection, first subcutaneously, later intravenously. In this animal the oestral reaction of the sex skin, while slight, did not progress in characteristic fashion. The lack of ovarian response in this case might be due in part to the exhaustion of the ovary which Hisaw, Hertz, et al. (1933), have shown occurs when only the follicle-stimulating fraction is used.

In a number of instances where luteinization has occurred, there has been a concomitant slight progestational change in the tube or the uterus. The nature of the experimental procedure, with removal of a control ovary and the subsequent checking of oestrin production in the second ovary by the pregnancy urine factor has resulted in uterine bleeding of oestrin privea. It appears that the secretion of progestin by the corpus luteum is either inadequate or is too much delayed to prevent the usual bleeding of oestrin withdrawal.

It is necessary to defer discussion of these instances of uterine bleeding to another time.

The combined action of these two substances on the monkey ovary does not appear to be of the nature of the "augmentation" effect of Evans, et al., or of Leonard, which has been obtained on the female rat.

In the first place an appreciable increase in size of the ovary does not occur. The action of the pregnancy urine factor seems actually to reduce the size of the ovary due to the involutional changes. In many animals this is not prevented by the simultaneous treatment with AP.

The luteinization which occurs appears to be due not to an augmentation of the reaction of one or the other principles, but is a response of two components of the primate ovary in a sequential manner. Follicular growth is in no instance accelerated by the addition of the pregnancy urine factor to the follicle-stimulating principle of the AP. The reverse invariably occurs.

Under the conditions of treatment it has been reasonable to believe that the AP factor maintained and matured the granulosa, and that the concomitant action of the urinary principle served to mobilize the thecal elements, the two progressing together into a new morphological unit, the corpus luteum.

In a single female monkey, My 140, 3250 gm., the combined use of the growth hormone (Squibb) and a pregnancy urine product (Antuitrin S) resulted in nothing but a typical PU reaction as previously described. Similar treatments of 30 days in three male monkeys gave no evidence of an accelerated action on the gonads.

In these limited experiments, it has been impossible to demonstrate a "super-additive" or "augmentation" effect in the monkey ovary.

SUMMARY

In previous reports evidence was presented indicating that the factor from human pregnancy urine which causes the ovarian response in rodents does not cause follicular activation in the rhesus monkey. The use of the extract results in involutional and regressive changes in the ovary. Relatively large doses, up to 9900 units, administered intravenously in adult animals causes slight lutein changes in the theca interna, but with progressive cytolysis of the granulosa and involution of all small follicles in all instances observed. There is a complete and immediate cessation of oestrin production.

The present experiments (nine animals) show that luteinization of the ovary of the rhesus monkey may be accomplished. In immature animals follicular activation and growth is induced by an AP extract. When an oestral skin is produced, in 6 to 8 days, an active fraction from urine of human pregnancy is combined with the AP and both administered intravenously, with, in certain instances, complete luteinization. Lesser degrees of response occur with subcutaneous administration.

The AP fraction used acts primarily on the granulosa, and the PU on the theca interna. The corpus luteum which is formed after simultaneous administration of the extracts is a result of the activation of the two components of the corpus luteum, theca and granulosa.

There is no evidence of an "augmentation" or a "super-additive" effect as a result of the combined treatment. The response is due to the synergistic action of two substances on the two participating components.

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THE SEX DETERMINATION TEST OF DORN AND SUGARMAN

REPORT OF 51 EXPERIMENTS

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Dorn and Sugarman, in a recent report (1), described a method for the prediction of the sex in the unborn. By injecting rabbits fully 3 months old, whose testicles were in the inguinal canal, with urine of women 5 months or more pregnant, they were able to prognosticate the sex of the unborn child in 80 (94 per cent) of 85 cases. The basis for their prognosis was the microscopic changes in the testicle of the rabbit noted 48 hours after injection. The testes of the rabbits injected with urine from women carrying an unborn female child were developed precociously, whereas those of animals injected with urine from women carrying an unborn male child were not so stimulated.

In a repetition of the work, Curphey and Romer (2) were unable to confirm the findings of Dorn and Sugarman.

The present observations were also carried out for the purpose of testing the validity of the Dorn and Sugarman conclusions.

MATERIALS

The 51 treated and 5 control rabbits varied in age from 77 to 106 days. Of the treated ones, 30 were 90 days of age or more. According to the requirements of Dorn and Sugarman, the testicles of all animals were in the inguinal canal, but contrary to their specifications, the rabbits were not all of the same breed.

The intervals in days between the dates of experiments and birth of children are summarized in Table I. It will be observed that all of the women were in the last two months of pregnancy when their urine specimens were tested.

TABLE I

Interval Between Experiment and Delivery	Number of Women
1–10 days inclusive	27
11–20 days inclusive	9
21–30 days inclusive	3
31–40 days inclusive	6
41–50 days inclusive	4
51–60 days inclusive	2
Total	51

There were 26 male and 25 female children born to the 51 women whose urine was tested.

The intravenous injection in each instance consisted of 10 cc. of filtered, morning urine* warmed to body temperature.

*The specimens of pregnancy urine were secured from patients in the University Hospital and the Philadelphia Lying-In Hospital through the courtesy of Dr. Edmund B. Piper and Dr. Norris W. Vaux.

TABLE II

Group	Animal Data				Human Data	
	Identification	Age	Spermatogenetic Activity in Testes		Interval Before Labor	Sex of Child
	Number	Days	Control	Treated	Days	
I—Double Control	59	78	○ ○	—	—	—
	60	78	○ ○	—	—	—
	45	80	○ ○	—	—	—
	26	86	+ +	—	—	—
	44	86	++ ++	—	—	—
II—Single Control	40*	70	○	○	⊙	♂
	53*	75	○	○	⊙	♂
	47	77	○	○	38	♂
	46	77	+	+ (–)	1	♂
	39	77	+	+	⊙	♂
	48	79	○	○	29	♂
	43*	80	○	○	1	♂
	19*	80	+	+	⊙	♂
	32	83	○	○	13	♂
	56	91	+	+	51	♂
	80	94	○	○	20	♂
	78	95	++	++ (–)	44	♂
	76	97	○	○	25	♂
	74	97	○	○	30	♂
	68	99	○	○	32	♂
	66*	106	○	○	38	♂
	70	72	○	○	9	♂
	18*	75	○	○	18	♀
	52*	76	○	○	9	♀
	24*	77	○	○	1	♀
	54*	77	○	○	⊙	♀
	55*	77	○	○	⊙	♀
	58	77	○	○	13	♀
	38	79	○	○	⊙	♀
	49	79	○	○	54	♀
	50*	79	○	○	⊙	♀
	51	80	+	+	⊙	♀
	41*	83	○	○	⊙	♀
	31	91	+	+	36	♀
	62	91	○	○	7	♀
	64*	94	○	○	9	♀
	81	95	+	+	13	♀
	79	95	+	+	4	♀
	61*	95	○	○	48	♀
	77	97	+	+	8	♀

TABLE II Cont.

Group	Animal Data				Human Data	
	Identification	Age	Spermatogenetic Activity in Testes		Interval Before Labor	Sex of Child
	Number	Days	Control	Treated	Days	
	71	97	++	++ (–)	41	♀
	72	97	+	+	33	♀
	75	97	○	○	13	♀
	73	99	○	○	3	♀
	67*	99	○	○	42	♀
	6 *	94	○	○	19	♀
III—No Control	84	94	—	+++ +++	10	♂
	85	94	—	+++ +++	1	♂
	86	95	—	++ ++	16	♂
	82	95	—	++ +	14	♂
	83	96	—	+++ +++	35	♂
	87	97	—	+++ +++	6	♂
	88	97	—	○ ○	6	♂
	89	97	—	++ ++	0	♂
	100	97	—	++ ++	1	♂
	90	97	—	+++ +++	2	♀

SYMBOLS. * Seminiferous tubule diameters measured and different kinds of germinal epithelial cells counted.
○ No spermatogenetic activity.
+ Slight spermatogenetic activity.
++ Moderate spermatogenetic activity.
+++ Extreme spermatogenetic activity.
(–) Less spermatogenetic activity than in other testis.
⊙ Interval between voiding urine and delivery less than 24 hours.
♂ Male.
♀ Female.

LEGEND. Results of histologic analysis of rabbit testes following intravenous injection of pregnancy urine. Group I. Experiments in which rabbits received no treatment. Group II. Experiments in which one testis was removed before injection. Group III. Experiments in which bilateral orchidectomy followed treatment.

Data arranged according to age of animal and sex of newborn child. Note the almost identical condition of spermatogenetic activity in control and treated testes in Group II.

METHODS

Three sets of experiments were performed: In the first (Table II, Group 1), no injections of urine were given. The two testes of each of five rabbits were merely removed 48 hours apart.

In the second set of experiments (Group II), one testis was removed from each of 41 animals and used for control. The intravenous injection was then made into the marginal ear vein and at the end of 48 hours the remaining testis was removed.

In the third series, 10 animals received urine injections 48 hours before bilateral orchidectomy was performed.

Operative procedures were carried out under ether inhalation anesthesia. The skin and coverings overlying the testicle were incised, and the testicle was delivered from the operative wound, its pedicle ligated and cut. It was fixed in Susa or Bouin solution, and cut into sections 6 μ. in thickness, which were stained with hematoxylin and eosin.

RESULTS

The experiments are summarized in Table II. This table includes: (a) Age of the rabbit. (b) Interval between day of experiment and day

of labor. (c) Sex of unborn child. (d) Results of the histologic analysis of the testes.

The data are arranged according to: (a) The three methods of experimentation; (b) the age of the animal; (c) the sex of the unborn child.

Histologic Analysis. Each testis was examined microscopically to determine: (a) The presence and degree of spermatogenetic activity; (b) the number of different kinds of germinal epithelial cells; (c) the diameter of the seminiferous tubules.

Degree of Spermatogenetic Activity. It was possible to classify all testes as exhibiting either (a) inactivity, (b) slight activity, (c) moderate activity, or (d) extreme activity.

Inactivity (Marked o in Table II). In these testes, almost all spermatogonia were in the resting state; a few were in the process of multiplication. Primary spermatocytes were extremely rare. The seminiferous tubules possessed no lumina.

Slight Activity (Marked + in Table II). A small group of spermatogonia were actually in the process of multiplication. Quite a few primary spermatocytes were present. Here and there a lumen existed in a seminiferous tubule.

Moderate Activity (Marked ++ in Table II). The tubular walls were lined with one complete and sometimes a second, but incomplete layer of spermatogonia, the majority of which were in the process of division. Primary spermatocytes were found quite frequently. Sometimes a few round cells were seen in the lumina of the ducts of the epididymis.

Extreme Activity (Marked +++ in Table II). Here the tubules were lined with one complete and a second incomplete layer of spermatogonia, with two to four additional layers of primary spermatocytes. In certain tubules, the spermatocytes were detached from the spermatogonia and occupied the center of the lumen. If not detached, the lumina were extremely narrow. Many round cells were seen in the ducts of the epididymis.

GENERAL OBSERVATIONS

Spermatogenetic activity was observed in the control testes of 14 (30 per cent) of the 46 animals in Groups I and II. It was present in spite of the fact that the testes of all of the rabbits were in the inguinal canals. If all of the 14 animals had been of one strain, this fact would have suggested that in this single breed, spermatogenetic activity might have begun earlier than in other breeds. However, the observation that these rabbits were distributed throughout several breeds indicates that spermatogenetic activity in the breeds employed does not start at a uniform time; and further, that there are marked individual variations. Therefore, it would seem that the position of the testis, with respect to the inguinal canal, bears no rela-

tion to the presence or degree of spermatogenetic activity. Individual variation in this respect also appeared to be considerable. For example, slight activity was found in the testis of one rabbit as early as the 77th day, whereas, the testis of another animal, 106 days old, was still inactive.

These observations indicate that only histologic analysis can give the necessary information for determining the presence and degree of spermatogenetic activity in the rabbit's testis. Consequently, it is necessary to study a control testis histologically before evaluating the degree of activity of a treated one.

In the 41 cases of Group II, control testes were available for microscopic examination. In 17 of these 41 cases, it was found that the animal had been injected with urine from women bearing a male child, and in 24 cases with urine from women bearing a female child.

The presence and degree of spermatogenetic activity were identical in both the control and treated testes of the animals in Group II. The treated testes never exhibited activity when the controls showed none, or, when activity was present in a treated testis, it was always equal in degree in the control testis. The treatment did not increase activity. In fact, the reverse seemed to be true. In three cases [Marked (—)] treated testes exhibited slightly less activity than their controls. These observations suggest that urine from pregnant women does not either incite or increase spermatogenetic activity in treated testes of rabbits from which a control testis has been removed prior to treatment.

In 16 instances (marked * in Group II), control and treated testes were studied with respect to (a) tubule diameter and (b) the number of the different types of germinal epithelial cells. In addition, the gross appearances of the testes in Group II were noted at the time of operation and protocolled but not recorded in Table I. None of these three methods of study gave evidence that the injected urine had a stimulating effect upon the testicle. There seemed to be no evidence in this entire series of observations (51 experiments) to indicate that the urine of the mother might be used for prediction of the sex of the fetus.

In the 10 cases in Group III, the urine was injected 48 hours before removing both testes at one operation. The testicles from one of these animals were inactive. The testes of four exhibited a moderate degree of activity. Since the latter amount was observed in some of the control testes of the animals in Groups I and II, the four instances of moderate activity in Group III would not necessarily point to a stimulating effect from the injected urine.

The testes from the remaining five animals in Group III, however, exhibited extreme activity. It was later found that four of these five rabbits had been treated with urine of women who were bearing a male child, and only one was injected with urine from a woman who was carrying a female child. These observations upon the 10 animals in Group III seemed to offer no basis for the prediction of sex.

The above mentioned five cases of extreme activity in Group III seemed to point to the existence of pregnancy. Hence, these observations would tend to confirm the single one of Curphey and Romer (2), which led them to state that the urine of pregnancy, irrespective of sex, may have a stimulating effect upon the rabbit's testicle and hence have some value as a specific pregnancy reaction.

The method has little significance to us as a means for the diagnosis of pregnancy: Only 50 per cent of the 10 experiments in Group III gave a positive result, whereas the remaining ones were either doubtful or negative. In view of these findings; because the pregnancies were all so well advanced, and because other biologic tests are of much greater known accuracy, this aspect of the reaction appears to be of little, if any, value.

SUMMARY AND CONCLUSIONS

Urine from 51 women in the last two months of pregnancy was injected intravenously into the same number of male rabbits of approximately three months of age, from several breeds.

Gross and microscopic examination of testes removed both before and after treatment gave the following results:

1. The urine injection had no appreciable effect upon the gross appearance of the testes, the diameters of the seminiferous tubules, or upon the number of different kinds of germinal epithelial cells.

2. In an insignificant number of instances the treatment may have initiated or increased spermatogenetic activity.

3. The testes of animals treated with urine from women who later were found to have given birth to female children exhibited the same microscopic picture as those testes from animals which were treated with urine from women who had later given birth to male children. From these observations it is concluded that the urine of pregnant women does not offer a means for predicting the sex of the unborn child by the rabbit testis reaction. The use of the testis reaction for determining the existence of pregnancy in the human would also seem to be of little, if any, value.

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OPTIC NERVE AND MYXEDEMA

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MONTEVIDEO

This report deals with certain disturbances of the nervous system which are not given in the classical descriptions of myxedema, but which are thought to be due to that disease. Alterations of the optic nerve in myxedema are rare. A case of this kind is described here, that of a female patient suffering from a slight myxedematous condition causing blindness through double optic neuritis which was successfully treated with thyroid extract.

CLINIC HISTORY

E. S. 24 years old was Spanish, married and had no profession. An accentuated obesity was the only morbid antecedent of any consequence. Her father weighed 114 kgm., her mother 100 kgm., and two brothers weighed 93 kgm. each. A sister and a younger brother weighed 113 and 119 kgm., respectively.

Three years before the patient had had a mild case of measles. She has never used tea, coffee, alcohol or any other toxic substance in excess. Her first menstruation, at the age of 20, was very abundant and lasted from seven to eight days. About seven years ago she complained of being chilly and suffered from accentuated drowsiness and frequent headaches. She became pregnant in July, 1910, and was surprisingly well during this period. Also, all the symptoms just described completely disappeared during pregnancy. On March 11, 1911, she gave birth to her first child, and was able to nurse him. However, after parturition she again began to feel a recurrence of her symptoms (headaches, chilliness and drowsiness). During her second pregnancy, early in 1912, these symptoms again disappeared. On October 28, 1912, she again passed through normal parturition. However, this was followed by slight metrorrhagia, which lasted about 13 days. Twenty days after parturition there was another hemorrhage, and finally menstruation appeared with normal characteristics, with the exception that the first period lasted about 10 days.

It must be borne in mind that from the first parturition on the hemorrhagic symptoms were intense. The steady increase of chilliness, drowsiness, and headaches during this period was also noted, as well as the fact that the hair was beginning to fall. Three months after partutition the patient began to notice a gradual reduction of vision in the right eye, which increased to such an extent that within a few days she could perceive only large objects close to her. Treatment with iodin was then adopted and some improvement was noted. It was possible for her to distinguish the large letters, if these were placed very near the affected eye. Two months later, however, this improvement disappeared.

The patient continued thus without presenting other new manifestations until early in 1917, when all these general troubles again disappeared on the occasion of a third pregnancy, followed by a normal parturition. After parturition, metrorrhagia again occurred. Nursing was normal, but the headaches, drowsiness, falling hair, chilliness and hemorrhages were accentuated. Three months and a half after the last parturition, the patient began to note a reduction in the vision of her left eye, and she consulted Dr. Demicheri on February 2, 1918. His report was:

"R. E. V.—Movement of the hand.

"L. E.—0-8-2 V 1/10. Loss of the lower visual field.

"R. E.—Atrophy of the papilla.

"L. E.—Papilla with diffuse margins."

The process went on so rapidly that an examination four days later by Dr. Vazquez Barriére showed the visual acuity of the left eye to be 2/60. The existence of atrophy of the right papilla, as well as the papillitis, was also confirmed.

The clinical examination at this time showed the patient to be in a good state of nutrition. She was a little pale, and her face suggested hypothyroidism. The eyebrows were scanty in the outer third. The thyroid gland was normal to palpation. With the exception of the lesion affecting the second pair of cranial nerves nothing abnormal was found in the nervous system. The right pupil was intensely mydriatic, and did not react to light. The left one reacted poorly to light and to accommodation. The heart and the vessels were normal. The pulse rate was 76, and the blood pressure was 110/50.

In the laboratory tests the urine was found to be normal. The blood Wassermann examination gave normal findings. The hematological investigation showed only a slight anemia.

The x-ray examination of the skull showed the anterior-posterior diameter of the sella turcica to be 9 mm. and the vertical diameter 10 mm. No deformation in the clinoid processes nor in the dorsum sella was noticed. The dimensions were normal, according to Kehler's dicta.

Since it was not possible to find a definite etiologic cause of this optic neuritis, and since the patient was diagnosed as being hypothyroid the use of thyroid extract was indicated. The results obtained were as follows: On the tenth day the obscure symptoms of hypothyroidism disappeared. At the same time the vision improved, the patient being able to perceive objects. On the twentieth day she could clearly distinguish the large letters held very close to her. At the end of a month she could read a newspaper and even write correctly. This improvement took place only in the left eye, for the right optic nerve was actually atrophied. When the thyroid extract was not used for some days the patient felt that her vision was diminished. An examination made on May 6 of the same year showed considerable improvement in the vision of the left eye, which was found to be 1/3. The papilla of this eye was whitish, but the papillary blur had disappeared. The visual field was almost normal to the white color, a little restricted to blue, even more so to red, and absent to green. No changes were noted in the right eye. Wishing to corroborate the patient's report, with reference to lowering of her vision when the thyroid therapy was postponed, it was found that five days after the treatment was discontinued (and this break began just after the last ocular examination) the visual acuity was lowered from 1/3 to 1/6. Readministration of thyroid extract again brought about improvement in vision, but as the patient left our country a few days later we could not follow closely the evolution of her affection. Therefore, the successful results of thyroid treatment, as well as the increase in the severity of the process when the drug was postponed, lead us to suspect the myxedematous origin of this neuritis. The absence of any other etiologic cause also substantiates this belief.

LITERATURE

Schmidt-Rimper (1) published the history of a myxedematous woman, presenting a bilateral central scotoma without any objective change of the papilla. He considered this case as being due to a retrobulbar neuritis. The patient improved with the use of thyroid extract. The available data are not sufficient to assert that the hypothyroidism was the basis of this ocular disturbance.

Sanesi (2) has published the history of a myxedematous man, presenting a bitemporal hemianopsia. The ophthalmological examination gave negative findings. Treatment with thyroid extract resulted, at the end of four weeks, in complete recovery of the patient from both his myxedematous and ocular disturbances. The author explains the visual disturbance as being due to a vicarious hypertrophy of the hypophysis, which thus pressed against the optic chiasm. This hypothesis is based on the fact mentioned by other authors, such as Abrikosoff (3) and Ponfick (4), who have found at the autopsy of myxedematous people, a hypophyseal hypertrophy even in those cases without any acromegalic symptoms.

Wagner (5) reported the case of a woman of 26 years of age who had had for some months a reduction of the vision of the left eye, and for two weeks a similar reduction in her right eye. In the left eye was found an atrophy of the optic nerve together with a visual acuity of 1/10, and a temporal hemianopsia. In the right eye there was neuroretinitis, with a visual acuity of 1/10. Wagner admits the existence of myxedema, but is not certain that there was not some associated acromegaly. The examination of the circulatory system showed no abnormalities. The urine was free of sugar and albumin. Thyroid extract was administered (0.30 cgm. daily). Ten weeks later the condition of the left eye was unchanged, but the visual acuity of the right eye was equal to one, and the ophthalmological examination showed that the neuro-retinitis had disappeared. The patient had lost 6 kgm. in weight, and the

general condition had improved. Wagner was of the opinion that the neuro-retinitis of the right eye was due to thyroid insufficiency and, perhaps, also to the hypophyseal disturbance, as well as disturbance of some other endocrine glands. He does not give his opinion as to the cause of the optic atrophy of the left eye with temporal hemianopsia, but he thinks that it was not due to the same cause as that producing the neuro-retinitis of the right eye.

First of all, it must be admitted that left eye optic atrophy with temporal hemianopsia, due to the pressure on the optic chiasm by the hypertrophied hypophysis has been demonstrated, just as it has been reported in pure myxedema and in co-existent acromegaly and myxedema.

Wagner was uncertain as to the co-existence of acromegaly in the case reported. The neuro-retinitis of the right eye could be explained either by the hypothesis of a pluriglandular dysfunction in which the thyroid insufficiency would have played an important part, as Wagner remarked, or by admitting that the hypophyseal hypertrophy itself could have produced the neuro-retinitis. We believe this latter hypothesis to be the more satisfactory.

It must be remembered that hypertrophy of the hypophysis does not always provoke the classically known ocular troubles of unilateral or bilateral temporal hemianopsia, but it also causes simple optic neuritis or retro-bulbar neuritis or even neuro-retinitis.

Johnston and Manro (6) have published a case of acromegaly in which the ophthalmological examination showed the same symptoms that were present in Wagner's case. In the left eye there was atrophy of the optic nerve, and in the right eye an acute neuro-retinitis. The autopsy showed the existence of a sarcoma of the hypophysis.

Thyroid extract gave Wagner successful results inasmuch as the ocular troubles were concerned, and this is not discordant with the theory of hypophyseal pressure since we have just mentioned the observations of Sanesi in which the bitemporal hemianopsia, clearly showing hypophyseal hypertrophy, disappeared after administration of thyroid extract.

Burchard (7) describes a myxedematous and acromegalic woman of 23 years of age, who presented a central scotoma and a pale right optic nerve.

Meyer (8) has observed the case of a myxedematous boy with optic atrophy and bitemporal hemianopsia relieved to some extent by thyroid extract. Meyer believed the atrophy to be due to pressure on the optic chiasm by the hypertrophied hypophysis.

Gourfein-Welt (9) has published the observation of a myxedematous and acromegalic woman of 47 years of age, presenting a slight left optic neuritis with temporal hemianopsia. The sella was enlarged. The patient improved with the use of thyroid extract.

Berliner (10) has published a case of myxedema with optic atrophy and bitemporal hemianopsia. The x-ray examination of the skull showed an enlargement of the sella. The author believes the ocular troubles of this patient to be due to the pressure on the chiasm through hypophyseal hypertrophy. The vision improved with the administration of thyroid extract.

Wilbrand and Saenger cite Surow's (11) case, referring to the history of a myxedematous and acromegalic woman. This patient presented an accentuated optic atrophy on the right side with a visual acuity of 1/8, and an incipient optic atrophy of the left eye with a vision of 20/70. Thyroid extract provoked a marked improvement of the right eye vision, while the left eye vision improved until it reached 20/40. The visual field was larger after treatment. Was this patient's optic neuritis due to a hypophyseal hypertrophy, or was it due to a myxedematous intoxication?

The absence of a temporal hemianopsia does not enable us to avoid consideration of the pressure mechanism exerted by the hypophysis on the chiasm. In fact, the optic neuritis without hemianopsia has been described in acromegaly as in the above mentioned case of Johnston and Manro. The improvement provoked by thyroid extract is not in discordance with the existence of the pressure mechanism exerted by the hypophysis, for this very same improvement has been observed in Wagner's and Sanesi's cases, in which hypertrophy of that gland clearly existed. Also, the reduction of the visual field observed in Surow's patient, has also been mentioned in acromegaly by Strzeminsky (12), Wittern (13), Praun and Pröscher (14) and Bichowsky (15). Thus, in spite of the impossibility of putting aside the pressure mechanism theory the toxic origin seems to be more plausible. Only the existence of acromegaly deters us from being more affirmative in this latter sense.

Derby (10) has published the clinical history of a patient 56 years of age in whom an ocular examination, made in 1902, showed that the vision with cor-

rection was 6/4 in both eyes. The eye fundus was normal. In August, 1919, the vision, with correction, was 6/10 in the right eye and 6/12 in the left. The ophthalmological examination showed the retinal arteries to be somewhat reduced and pale. On October 13, 1910, the vision, with correction, was 6/60 in the right eye and 6/15 in the left. The ophthalmological examination showed an accentuated atrophy of the right optic nerve and a slightly pale left papilla. There was a slight bitemporal defect in the visual field. In January, 1912, there was a clearly established bitemporal hemianopsia. Derby states that the patient improved on thyroid extract, but he does not specify whether he means the general condition or the vision. He believes the troubles all to have been due to the hypophyseal hypertrophy. This same author has also described the history of a myxedematous male patient, aged 49, presenting the symptoms of thyroid insufficiency of ten years' standing. The blood Wassermann examination was negative, and the x-ray examination of the skull showed nothing abnormal. The vision, with correction, was 6/30 on the right side and 6/12 on the left. The margins of the papillas were diffuse. A further examination showed that the right eye vision was 6/60, and in the left eye 2/60. The ophthalmological examination showed that the right papilla was grayish and the arteries very thin. The left papilla was even paler, with diffuse margins and choroid atrophy. The right visual field was concentrically reduced to 22 degrees. The left visual field was reduced to a 5 degree diameter, towards the nasal side from the center. Due to the choreo-retinitis presented by this patient Derby believes that the intervention of a pressure mechanism exerted by a hypertrophied hypophysis is not very probable. He suggests the possibility that the choreo-retinitis is due to a toxemia of myxedematous origin. However, he has not thoroughly eliminated the possibility of a syphilitic process, causing the affection, and his patient has thus been treated with mercury and iodin. The author does not indicate whether or not the patient was given thyroid treatment. For this reason it is doubtful whether there is a myxedematous origin of the ocular troubles.

Avizonis (17) has described the history of a myxedematous male patient of 50 years of age, presenting a bilateral optic atrophy. In the right eye, in which the vision had not thoroughly disappeared, there was a temporal hemianopsia. The author believes this optic atrophy to have been due to a vicarious hypertrophy of the hypophysis exerting its pressure on the optic chiasm.

With the exception of Schmidt-Rimper's case and Derby's second observation, we believe that in all the cases cited there was an unquestionable connection between the optic nerve disturbances and the myxedematous condition. In almost all of the cases there was optic neuritis. In Wagner's case there was neuro-retinitis. In Berliner's and Meyers' cases there was noted a bitemporal optic atrophy. In our own case (18), there existed, on one side an optic neuritis, and on the other an optic atrophy. The examination of the visual fields showed the existence of unilateral or bilateral temporal hemianopsia in seven patients [Sanesi, Meyer, Wagner, Gourfein-Welt, Berliner, Derby (first observation) and Avizonis]. In Surow's patient, in whom the myxedema was associated with acromegaly, the visual field was concentrically reduced, a condition already mentioned by Strzeminsky and other authors in studies on acromegaly. In Burchard's patient, presenting myxedema with associated acromegaly, there was a central scotoma in a total of 22 cases of hypophyseal tumors coming to autopsy. In spite of the fact that in the cases of Burchard, Surow and Gourfein-Welt the myxedema was associated with acromegaly we have included them in this report because of the successful results of thyroid treatment in the patients of the latter two authors. It may be assumed, as a mere hypothesis, that the hypophyseal hypertrophy observed in these patients was due in part to the anatomical changes caused by acromegaly, and partly to a vicarious hyperthophy of this gland, due to myxedema. The improvement of the thyroid insufficiency by the corresponding opotherapy would exclude this second element of hypophyseal hypertrophy and would thus easily explain the improvement of the ocular disturbances.

What then is the pathogenesis of the optic nerve alterations present in myxedema? These alterations may be due to two mechanisms: The first is due to pressure exerted through the hypertrophied hypophysis. The second is of a toxic origin. The first mechanism may be due to a vicarious hypertrophy of the hypophysis (and this has been demonstrated by the anatomical studies of Abnikosoff and Ponfick) in the cases of pure myxedema or to proper alterations of acromegaly when both diseases are associated. The toxic mechanism is of endocrine origin and would cause optic neuritis through the humoral way. The mechanism of the pressure may logically explain eight of the cases we have just reported [Sanesi, Wagner, Burchard, Meyer, Gourfein-Welt, Berliner, Derby (first observation) and Avizoni]. Thyroid extract has brought about an im-

provement, or recovery, from ocular disturbances in six of these eight cases. In Burchard's, Avizoni's and Derby's second observation no mention is made of thyroid treatment. It would thus appear that the toxic element was responsible for the optic nerve alteration in our own case, and in that of Surow, although, as previously stated, the existence of acromegaly in the latter case prevents a more affirmative statement.

In regard to our own observation, the myxedematous origin of the optic neuritis is not only demonstrated by the success of thyroid treatment but also by the reduction of the visual acuity noted some days after stopping treatment, and by the improvement when the treatment was again instituted. The diagnosis of our case has been confirmed by eliminating, after a careful clinical study, all other etiologic factors and by the aid of the laboratory tests previously mentioned. The course of the disease proved, too, the exactness of this diagnosis. Fifteen years after leaving the hospital our patient is perfectly well because the thyroid treatment is being carefully followed. This would seem to eliminate, therefore, the intervention of any other etiologic agent in the production of the patient's optic neuritis. The absence of acromegalic symptoms, as well as the normal dimensions of the sella shown by the x-ray examination of the skull, and the absence of hemianopsic disturbances, confirm, too, the toxic origin of this neuritis.

The interest of this observation chiefly rests in the fact that, according to our personal knowledge, it is the first to be reported in which it has been clearly demonstrated that the toxic element associated with myxedema may cause optic neuritis.

SUMMARY

The case is reported of a woman of 24 who developed symptoms of thyroid deficiency with headaches, chilliness and drowsiness. During two pregnancies the symptoms disappeared but promptly reappeared after parturition. Marked reduction of vision then occurred which improved temporarily under iodin therapy. After a third parturition more marked reduction of vision occurred associated with right papillary atrophy and left papillitis. X-ray examinations gave no evidence of pituitary hypertrophy. Under thyroid medication the vision markedly improved. Remissions in the medication were followed by renewed loss of visual acuity. The neuritis is therefore ascribed to a myxedematous origin.

The pertinent literature is reviewed and discussed.

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FAMILIAL INFANTILISM DUE TO HYPOPHYSEAL AND THYROID INSUFFICIENCY

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MONTEVIDEO

This report concerns five patients, a brother and four sisters who were diagnosed as suffering from infantilism due chiefly to hypophyseal insufficiency. The outstanding clinical features observed in these patients were: reduction of size of the body, atrophy of the sex organs, absence of mental retardation and delayed epiphyseal closure. In Figure 1 may be seen three of the five patients mentioned, showing their relatively short stature as compared with the other three members of the family.

Figure 1. Three of the five patients with three other members of the family.

The etiology of this affection cannot be charged to insufficiency of the thyroid gland because of the absence, at the onset of the illness, of any deficiency either in walking, in speech or in mental activity. Thus it would appear that the trouble is due primarily to intervention of the anterior lobe of the hypophysis. However, thyroid insufficiency, as will be discussed later, does play a rôle in this clinical picture and in this case, therefore the patient's trouble is of a double endocrine origin.

Because of the somewhat senile aspect of their skins, which gives to some of these patients an oldish, heavy, care-worn appearance, the term infantilism seems hardly correct. The term dwarf-infantilism would seem

more clearly to describe the syndrome but the precise terminology is not important. In this report the term "infantilism" is used. Such writers as Bauer have grouped under the exclusive term of infantilism a few cases of hypophyseal infantilism in which the skin was senile and gerodermal in type.

CLINICAL HISTORY

I. B., male, single, aged 47. (Figures 1, 2 and 3).

Family History. The patient was not aware of the cause of death of his parents. They had been of normal height. The patient was the eldest of eight brothers; three of the brothers were of normal height and aged 45, 42 and 32; the other brothers were of low stature. Their respective ages were 38, 36, 33 and 26. A cousin of their father was very tall and presented signs of acromegaly.

The patient complained of muscular and articular pains, hemorrhoids, slight constipation, diminished perspiration and chilliness.

Figure 2. Patient I. B.

Clinical Examination. The height was 128 cm., and the weight 40 kg. The skin was dry and pale and showed in certain areas a fine branny desquamation. The lower eyelids were slightly edematous and baggy. The tongue was normal. The hair was abundant and silky. Body hair was absent, including that of the pubic and axillary regions. The subcutaneous fat was especially abundant in the abdomen and thorax. The breasts were developed. There was a marked genital infantilism. The penis was small, its length being 3 cm. The scrotum was infantile. The testicles were small and atrophied and could be palpated in the inguinal canal. A slight kyphosis of the superior dorsal region was observed. The x-ray examination showed a somewhat accentuated high dorsal scoliosis.

Nervous System. The tendinous and cutaneous reflexes were normal, as was also the rest of the nervous system.

Mental Examination. The mental status was normal according to age.

Circulatory System. The heart was normal. The pulse rate was 62, and the maximum blood pressure was 150 mm.

ANTHOPOMETRICAL MEASUREMENTS

(According to Viola)

Height	1 m.	28 Cms.
Length of the sternum		16 "
Xypho-epigastric length		11½ "
Pubic-epigastric length		14 "
Length of the lower limbs		64 "
Length of the upper limbs		43½ "
Thoracic-transverse diameter		20 "
Thoracic-posterior diameter		16 "
Hypochondriac-transverse diameter		21 "
Hypochondriac antero-posterior diameter		18 "
Pelvic transverse diameter		23½ "
Limbs value		107½ "
Thoracic value		5.120 "
Upper abdominal value		4.347 "
Lower abdominal value		5.922 "
Total abdominal value		10.269 "
Trunk, total		15.389 "
Abdominal total length		25½ "
Jugulo-pubic length		41½ "

Skull and Face

Glabellar antero-posterior diameter	19 "
Maximum transverse diameter (biparietal)	15 "
Total circumference of the skull	54½ "
Bizygomatic diameter	13½ "
Occipito-glabellar length (measurement of the arch)	30 "
Cranial index $\frac{15 \times 100}{19} =$	78.9 "
Total length of the face	11 "
Naso-alveolar length	6½ "
Auriculo-vertical diameter	14½ "

SPECIAL EXAMINATIONS

Ophthalmological Examination. October 6, 1932. Vision: R. E. (deficient). L. E. (deficient). Slight direct astigmatism. Pupillary reactions were normal. Fundus was normal. Tension (Schiötz's instrument): R. E., with 7. 5 gm.=7=23—. L. E. with 7.5 gm.=7=23. October 18, 1932. Vestibular examination: Normal. October 10. 1932. Visual field: Perfectly normal.

Colon examination (on the same date) shows nothing abnormal with reference to the anatomical position.

Electrocardiographic Tracing. October 6, 1932. This examination showed a regular sinusal rhythm with a rate of 50 beats to the minute. Auriculo-ventricular conduction was normal.

Urine findings (made twice), were normal.

Basal Metabolic Rate. October 4, 1932, was minus 35.3 per cent. On November 30 of the same year this rate became minus 10.9 per cent after treatment with 0.15 gm. of thyroidin daily.

ROENTGENOGRAPHIC EXAMINATION

Skull. This examination showed the osseous conduit corresponding to the middle meningeal artery to be much enlarged. The cranial sutures were separated, especially the occipito-parietal and the parieto-temporal ones. (Fig. 4.)

The sella was somewhat large in proportion to the dimensions of the skull. The dorsum sellae was thicker and higher than normal. The sphenoidal sinus was normal in size and shape. No shadow of the frontal sinus was visible.

The impressions digitatae were absent.

The vertical rami of the lower jaw were short.

Forearms and Hand Bones. The epiphyseal closure was delayed in the distal ends of radius and ulna. Hypercalcified foci could be observed at the light zone between the osseous tissue and the cartilage.

Delayed closure was also to be observed in the distal end of the 2nd, 3rd, 4th and 5th metacarpals, as well as in the proximal end of the first 5 phalanges.

Legs. The upper tibial epiphysis was found to be only partially fused, and a part of the cartilage was still visible.

In the upper end of the fibula a line was observed, indicating the site formerly occupied by the cartilage, which had disappeared. The same finding was made in the lower epiphysis of the femur.

The patient has four sisters suffering from a similar condition. Their breasts were but slightly developed; the pubic and axillary hair was scanty and menstruation had not appeared. The basal metabolic rate of one of them (Inocencia), aged 36, was —32.2 per cent. Her height was 127 cm. and her weight was 23 kg. Another sister (Demetria), aged 33, had a basal metabolic rate of —26.3 per cent. Her height was 142 cm. and her weight

Figure 3. Skiagram of skull (Patient I. B.).

was 39 kg. The roentgenographic examination of this patient showed an absence of the frontal sinus. The sella was normal in size and shape. The impressions digitatae were absent. The distal end of the radius showed persistence of the fusion line. The basal metabolic rate of a third sister (Elisa), aged 26, was —24 per cent. Her height was 126 cm. The fourth sister was of the same infantile appearance but she could not be thoroughly examined. Her height was 142 cm.

We would seem to be dealing, therefore, with a case of familial infantilism from endocrine deficiency due chiefly to hypophyseal insufficiency

with thyroid involvement. The absence of mental retardation as well as of any delay in beginning to walk and to talk were the reasons for exclusion of thyroid insufficiency as a principal cause of the dystrophy. We believe, however, that the lowered metabolism in these patients is due to thyroid insufficiency. Improvement was noted in patient I. B. when given a course of thyroid treatment (0.15 gm. thyroidin daily). Under the same treatment administered over a period of two months the metabolic rate of one sister (Demetria) increased to +1.5 per cent and the rate of another sister (Elisa) was raised to —9 per cent. It was not possible to determine whether this thyroid insufficiency was due to diminished stimuli of the hypophysis or not. The hypophyseal insufficiency was characterized by the small stature and by atrophy of the sex organs in patient I. B. and by

Figure 4. Skiagram of hand and of knee (Patient I. B.).

the absence of menstruation in the sisters, (Genital examination was not made in the female patients). The thyroid insufficiency was chiefly typified by the extreme dryness of the skin and the excessive sensibility to cold. This latter was benefited by the administration of thyroidin.

What is the cause of this dystrophy? The familial character of the illness impels us to consider the cause as being chiefly of constitutional origin. It should be remembered, however, that in certain familial hypophyseal dystrophies the cause is not always hypophyseal imbalance for in a few cases reported the hypophyseal alteration was due to hydrocephalus (compression of the hypophysis through the floor of the third ventricle).

The x-ray examinations of our patients, however, gave no hint of intracranial hypertension. This again leads us to believe that the dystrophy

here is due to hypophyseal imbalance coupled with an associated thyroid involvement.

SUMMARY

A report is made of five patients, a brother and four sisters, who were diagnosed as suffering from infantilism due chiefly to hypophyseal insufficiency. The outstanding clinical findings were: small stature, atrophy of the sex organs in the male, absence of menstruation in the females, delayed epiphyseal closure, marked dryness of the skin, excessive sensitivity to cold and low basal metabolic rates. After a course of thyroid treatment in three of the patients the basal metabolic rate was increased in each of the three and there seemed to be less sensitivity to cold. These considerations led the authors to conclude that thyroid insufficiency played a secondary rôle in the illness.

UTERINE REACTION TO SEX HORMONES IN THE IMMATURE GUINEA PIG*

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Unlike the rat and the mouse the guinea-pig does not readily respond to manipulation with either the ovarian follicular hormone, theelin, or the anterior pituitary-like hormone, prolan. Aside from the element of species difference one explanation may lie in the longer sex cycle, implying a more complex genital mechanism. In order to record the behavior of the guinea-pig, which undergoes the same rhythmic changes in its reproductive tract observed in other animals, a study was made of 150 immature females weighing from 165 to 300 gm., injected with the following substances: pregnancy urine, male urine, commercial theelin (three preparations), theelol, commercial prolan (two preparations), sheep pituitary gland emulsion, pregnancy blood, and a few combinations of these.†

The major part of the investigation was devoted to the induced uterine hypertrophy which was striking and rapid, even though not constant in occurrence. Although enlargement of the uterus is one of the manifestations of oestrus in rodents, in the guinea-pig the increase in size was out of all proportion to the other changes and was often enormous. The method of arriving at an index of uterine hypertrophy has already been presented in a preliminary report (1). It consists, briefly, of dividing the weight of the trimmed supracervical uterus and adnexae, in milligrams, by the weight of the intact animal, in grams, which gives a workable ratio. All control animals had a ratio below 2.0, but 2.5 was taken as the lowest indication of hypertrophy. This value coincides with the figure of 1/400 in mice reported by Siddall (2). Where "positive" is used here, a ratio of 2.5 or over was measured, that is, definite hypertrophy; while a ratio less than 2.5 is described as "negative." The following condensed protocols summarize the results obtained.

Samples of urine of 14 women in the last month of pregnancy were injected into 26 animals. One sample proved fatal to the guinea-pig in which it was injected; one sample gave negative results in two animals. Two samples each gave negative results when 4.0 cc. were used but definite positive results with 6.0 cc. Among the other animals the dosage varied between 3.0 cc. and 13.0 cc., the duration of the experiment from 1 to 7 days. All results were positive, the ratios falling between 2.6 and 8.7 (sic).

The presence of the oestrus-producing hormone in some male urines has been definitely proven (3). Hence it was not surprising that two samples were positive in three guinea-pigs, while two samples were negative in three tests.

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†Appreciation is expressed to Parke, Davis, and Co. for a generous supply of Theelin, Theelol, Antuitrin-S, and Pituitary of Sheep; and to E. R. Squibb and Co., for Amniotin and Follutein.

One of the older crystalline preparations of theelin (commercial) was tested on six animals. The dosages were: 5, 9, 10, 20, 35, and 90 units. The corresponding ratios were: 2.0, 2.6, 2.6, 2.6, 3.5, 3.0. There is a suggestion here of a threshold type of reaction, an observation made in the work with pregnancy urine.

A more recent commercial preparation of theelin, crystalline, purified of most of the theelol, was injected into 23 animals. Uterine hypertrophy appeared irregularly, namely, with 50, 400, and 400 units, while 50-100 units caused no reaction in the others.

Of nine animals injected with theelol, two reacted positively after dosages of 2 cc. and 4 cc., the former undergoing oestrus. The other seven with 1 to 3 cc. gave negative findings, although the two injected with the smallest amount presented typical oestrus.

Another commercial preparation of theelin from amniotic fluid, in a lipoid solvent, was used. Of 13 animals injected, four responded with uterine hypertrophy (25, 50, 50, 200 units), while the others (50-200 units) did not.

Two commercial preparations of prolan were injected into 20 animals. In the one group (13 animals) positive results were obtained after the injection of 40, 120, and 200 units with no reaction following the use of 20 to 400 units. In the other, 200 units produced an effect in one animal, while 50 to 200 units gave negative results in the remaining six. Neither oestrus nor ovulation occurred.

An emulsion of the whole anterior pituitary gland of sheep was employed in six guinea-pigs. Hypertrophy was produced in one by the use of 7 cc., but 0.5 cc. to 10.0 cc. failed of effect in the others.

Blood serum of 15 pregnant women near term produced a rather paradoxical result in 25 animals injected: Two samples gave negative results with 2.0 and 5.0 cc.; two samples positive with 2.0 cc.; two samples positive with 2.0 cc., but negative with 5.0 cc.; five samples negative with 5.0 cc. When mixtures of four samples were tried in 10 guinea-pigs, three were positive with 2, 3, and 4.5 cc., while 1 to 5 cc. produced no change.

With the great irregularity of results observed in the preceding work it was not expected that many conclusions might be drawn from experiments with mixtures of substances unless a very large series were investigated. When either male or pregnancy blood serum was combined with small quantities of theelin a uterine hypertrophy followed in each of six animals, but no oestrus. When theelin and prolan were combined in five guinea-pigs uterine hypertrophy appeared three times, once with oestrus and once with simple opening of the vulva. In the two negative cases, oestrus, judged by vaginal smears, appeared once.

In no animal of the entire series, even those injected with large doses of sheep pituitary gland emulsion or with prolan was true ovulation observed. However, microscopic study, reported elsewhere (4), revealed extensive luteinization of cells of the theca interna and of undifferentiated cells throughout the ovary.

The injections had been so arranged that certain factors might be controlled and investigated: The weight of the animal, provided it was still immature, seemed utterly immaterial, corroborating in guinea-pigs the findings of Marrian and Parkes in mice (5). The intraperitoneal route had no apparent great advantage other than allowing the injection of greater quantities of material; toxic effects were not decreased by subcutaneous injection. The distribution of inoculations and the time of sacrifice did not play a very definite part in the result. Reactions appeared as early as 18 hours after injection in a few animals which died at that time from toxicosis or occasionally peritonitis, but animals spared till the sixth day showed no greater or different response from those killed 48 hours after the

first treatment. With urine and blood, the effective dosage depended naturally on the concentration of the hormone. Since this is variable among different samples, without an assay of each sample, little may be said. But it was apparent both with pregnancy urine and with a standardized theelin preparation that reactions were of a threshold nature and that the degree of uterine hypertrophy was independent of supra-liminal dosage.

The changes in the uteri of animals treated with theelin in one or another form were not remarkable qualitatively. The endometrium was thicker, the glands deeper and a little more tortuous than normal and the vessels were more abundant and congested. There was little stratification or evidence of a progestational state. On the other hand, the muscularis was enormously hypertrophied. In some animals the vagina showed typical oestrus changes; in others there was evidence of tumefaction and mucosal activity; in most the vagina was characteristic of the immature female. The surprising observation was made that opening of the vulva, oestrus, and

Figure 1. Uterine hypertrophy. The smaller uterus (and adnexae) is from a control guinea-pig weighing 304 gm., the "ratio" being 2.3; the larger is from an animal weighing 265 gm., injected with 13.0 cc. of pregnancy urine and killed on the sixth day; "ratio," 8.7.

uterine hypertrophy were not necessarily associated as a result of treatment. For example: uterine hypertrophy was accompanied by true oestrus in but two cases; by simple opening of the vulva with histological pre-oestrus changes, four times; a "negative" uterus, i.e., an index below 2.5, with true oestrus by the smear method occurred three times; simple opening of the vulva with a "negative" uterus was seen once following the injection of low titre pregnancy urine.

The threshold type and the great speed of the uterine reaction are worthy of note. The dissociation of effects on the different parts of the genital tract and the irregular action of theelin-bearing substances on uterine hypertrophy are matters of speculative interest. Evidence has accumulated that there is a biphasic control of the genital tract; certain reactions are the result of complementary treatment, others are withdrawal phenomena. Can it be shown that the genital tract tissues have a susceptible and a refractory period as a result of the particular preceding endocrine

action? To account for these observations, and others, on this basis, there must be postulated prepubertal waves of hormonal stimulation. It is unlikely that we are dealing with a multiplicity of hormones highly specific to the various parts of the genital tract; the evidence points rather to a threshold of reaction in the individual tissues.

SUMMARY

There are presented some of the results of injection experiments in 150 immature female guinea pigs, using the urine of pregnant women and commercial preparations of the sex hormones.

The more noteworthy observations are: (1) great irregularity of response; (2) enormous and disproportionate uterine hypertrophy appearing as early as 18 hours; (3) the threshold nature of the genital tract reactions; (4) an apparent dissociation in the occurrence of effects in the vulva, vagina, and uterus.

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Abstract Department

Relation of suprarenal cortex to myasthenia gravis pseudoparalytica (Frage der Beziehung der Nebennierenrinde zum Krankheitsbild der Myasthenia gravis pseudoparalytica). Bernhardt, H. and S. L. Simpson, Klin. Wchnschr. **11**: 2069. 1932.

The authors report a series of eight cases of myasthenia gravis pseudoparalytica, five females and three males. Six cases were classified as mild or moderately severe and were not treated. The two severe cases, females, aged 26 and 24, respectively, were treated with 5, 10, 15 cc. of eucortone per day. The total amount given to each patient was 120 cc. of extract. With some of the extract they obtained adrenaline-like effects (tachycardia, etc.) and occasionally when larger doses were administered a protein-like reaction occurred. No change occurred in blood sugar, calcium, or B.M.R., but the blood cholesterol was raised. The authors conclude that eucortone was apparently without effect in myasthenia gravis, and that there is apparently no etiological relationship between adrenal cortex and myasthenia gravis.—G. W. Thorn.

The relationship of the adrenal and thyroid glands to excised muscle metabolism. Davis, J. E. and A. B. Hastings, Am. J. Physiol. **105**: 111. 1933.

The metabolism of the excised abdominal muscle of mice was determined in terms of cubic millimeters per milligram of dried tissue per hour under the following experimental conditions and with the following results: (1) The excised muscle metabolism of 43 mice was determined at various intervals from 11 to 111 days after bilateral adrenalectomy and compared with that of their litter mate controls. The 18 cases that fell in the 40 to 70-day period after adrenalectomy had a mean oxygen consumption value of 6.23, whereas that of their litter mate controls was 4.62. The difference of the means, 1.61, appears significant, since its probable error is only 0.17. Before and after the 40 to 70-day period there was no significant difference in the oxygen consumption values of the two groups. (2) The excised muscle metabolism of 12 mice was determined at various intervals from 16 to 92 days after bilateral thyroidectomy and compared with that of their litter mate controls. The mean oxygen consumption value of the thyroidectomized group was 4.07; of the control group, 6.02. The difference of the means, 1.75, appears significant, since its probable error is only 0.20. (3) The excised muscle metabolism of 13 mice was determined at various intervals from 50 to 70 days after adrenalectomy following previous thyroidectomy, and compared with that of their litter mate controls. The mean oxygen consumption value of the thyroidectomized-adrenalectomized group was 5.69; of the control group, 5.90. The difference of the means, 0.21, being of the same order as its probable error, 0.17, could not be considered significant. (4) The excised muscle metabolism of 12 mice was determined after thyroxine administration and compared with that of their litter mate controls. The mean oxygen consumption value of the thyroxine-treated group was 6.74; of the control group, 5.01. The difference of the means, 1.73, appears significant, since its probable error is only 0.20. (5) The excised muscle metabolism of 12 adrenalectomized mice was determined after thyroxine administration and compared with that of their unoperated, thyroxine-treated litter mates. The mean oxygen consumption value of both groups was approximately 6.75, but that of the experimental was less during the first 26 days, and greater during 38 to 74 days after adrenalectomy than that of the control group. (6) The oxygen consumption of 13 intact mice was determined, first, before, and second, 43 to 65 days after, adrenalectomy, and compared with that of their litter mate controls. The oxygen consumption of the excised muscle of both groups was determined immediately after the second of the two former determinations. The mean oxygen consumption of the intact control mice and of the experimental mice before adrenalectomy was 37.5, whereas that of the experimental group after adrenalectomy was 44.0 liters per kilogram of body weight per 24 hours. The mean oxygen consumption of the excised muscle of the experimental group was 5.12; of the control group, 4.37. The increased oxygen consumption of the experimental group was 17.8 per cent in the latter case, and 16.9 in the former. The oxygen consumption of the 6 groups of control mice has varied from

4.37 to 6.02. When the 6 groups are taken as one, its standard deviation is not greater than that of some of the component groups, so that the total variability is not greater than might be expected in a group of this increased size. The variability may be due (in part) to differences in age and season, but more especially to the different times taken in the preparation of the excised muscle for the experiments. The results of the 6 series of experiments would appear to indicate that the increased metabolism following adrenalectomy of mice is a physiological attempt toward compensation of adrenal insufficiency by an increased production of thyroid hormone, and that this compensation continues until accessory adrenal tissue develops sufficient activity to make further compensation unnecessary. That this increased activity of mouse thyroid is not noticed until 40 days have elapsed may be due to the fact that mice are very resistant to the metabolic effect of thyroxine, since they require as much as a rabbit 75 times as heavy in order to produce a corresponding effect.
—Authors' Abst.

Adrenal cortical hormone and tissue respiration. Dye, J. A., Proc. Soc. Exper. Biol. & Med. **30**: 1223. 1933.

The oxygen consumption of surviving muscle fasciculi, with or without artificial substrates, was not altered by intraperitoneal injections of 5 to 10 cc. of eschatin (Parke, Davis & Co.) into living animals. The average values for 7 eschatin treated and 2 control animals were 1.97 cm. and 1.98 cm. per gm. of dry tissue per hour, respectively. In similar tests with 2 totally adrenalectomized cats at the height of adrenal insufficiency, a decrease in oxygen consumption was observed when no artificial substrate was supplied; but when sodium lactate was added to the suspension fluid, the oxygen consumption equalled that of normal animals' muscles under the same conditions. It was concluded that the action of the adrenal cortical hormone on tissue metabolism is not a direct one on the oxidation-reduction processes, but probably an indirect one involving the glycolytic phase of muscle metabolism.—Author's Abst.

Metabolic investigations on the hormone of the adrenal cortex (Stoffwechseluntersuchungen über ein Hormon der Nebennierenrinde). Harrop, G. A., H. Widenhorn and A. Weinstein, München. med. Wchnschr. **79**: 171. 1933.

The authors studied the metabolic changes in patients with Addison's disease and in adrenalectomized dogs. They noted the following effects: Increase in nitrogenous substances in the blood; decrease in the basal metabolic rate; decrease in blood pressure (not constant); marked change in excretion of nitrogen and in composition of the blood; no change in creatine or creatinine in either blood or urine until just before death; low blood sugar (not constant); diureses—not present during insufficiency but returning during first days of improvement; albuminuria sometimes present, and remaining for some days after recovery from insufficiency. They believe that the adrenal cortex influences the function of the kidney especially in regard to water and nitrogen elimination; that this effect is independent of the changes in circulation or blood pressure; that the evidence seems to point toward the specific influence of adrenal cortex hormone on kidney activity.—G. W. Thorn.

Hyperemesis gravidarum treated as a temporary adrenal cortex insufficiency. Kemp, W. N., Canad. M. A. J. **28**: 389. 1933.

Hyperemesis gravidarum is considered as due to a relative insufficiency of maternal cortico-adrenal secretion, and it is claimed, on the basis of results with 8 cases, that (until such time—presumably about three months—as there is compensatory hypertrophy of the maternal adrenal cortex) oral ingestion of a potent desiccated extract of beef adrenal cortex is effective in preventing and curing early cases of this condition.—A. T. C.

Temperature studies in normal and suprarenalectomized rats. Martin, S. J. and F. Maresh, Am. J. Physiol. **105**: 273. 1933.

Albino rats ranging in age from 2 to 20 months were picked at random from three different strains. Single determinations of the colonic temperature (thermo-couple in colon or vagina) and body weight were made on 193 males and 438 female rats during a period of 18 months. In a small group of females, vaginal temperatures and smears were also recorded. The colonic temperature readings of the females distributed around 38.2° C. with one-half ranging

between 37.8° and 38.7° C. The temperature in males was slightly lower. The extreme limits of all the temperatures were 36.5° C. and 39.5° C. The vaginal temperature was always 1° C. below the colonic. The different stages of oestrum showed no correlation with the vaginal temperature. In both males and females, the temperature distribution was the same for variations in weight, age, colony, season and time of day. A group of 162 rats from 3 different strains was suprarenalectomized bilaterally. The most probable survival period was 15 days with one-half of the number of animals dying between the 12 and 18 days. Ninety-five per cent died after complete suprarenalectomy. Smears of the vaginal contents of all females and colonic temperatures and body weight of a group of 75 male and female rats were made for a period of 9 to 14 successive days prior to any treatment to establish normal curves. Of these, 53 were completely and 22 unilaterally suprarenalectomized. In addition 9 controls were subjected to splenectomy and unilateral extirpation of the thyroid, supranenal, ovary and uterus. The colonic temperature in rats following complete suprarenalectomy remained normal for a relatively long period until 24 to 72 hours before death; in about one-third of the cases, the fall in temperature in the terminal stages was precipitous in nature. No relationship was found between the semi-comatose condition of a dying animal and any given temperature reading. All control animals showed a normal temperature throughout the experiment. Colonic temperature readings made at 2.5 minute intervals, were taken during a 10 to 20-minute control period, during the etherization until the recovery, or impending death of the animal. At least 50 control rats were subjected to 10-minute etherization. The rate of temperature decline during the etherization was quite constant for all rats and runs. At the end of a 10-minute depression period the temperature fall was 1.5° to 2.5° C.; the maximal depression of the temperature varied from 2.0° to 4.0° C. and was attained in 20 to 30 minutes. After the maximal fall, the temperature rose gradually to or slightly above the preliminary control level in 90 to 120 minutes. In all cases of control rats, a normal recovery of the temperature was noted within two hours. Successive daily etherizations of these animals did not influence their ability to recover from an experimental decrease in body temperature. The behavior of the colonic temperature of 37 suprarenalectomized rats after a 10-minute etherization was found to be as follows: (1) 8 rats showed a typical normal recovery within 2 hours; (2) 4 rats showed a delayed recovery; (3) 17 attempted a recovery but died, and (4) 8 animals died with no attempt at recovery. The ability to recover from an experimental fall in body temperature in rats of groups 3 and 4 was definitely impaired. A few results suggested that the longer the period after complete suprarenalectomy, the weaker the resistance of the animals toward an induced fall in body temperature. The cortical secretion of the suprarenals is related to the maintenance of body temperature only in so far as its presence is concerned with the normal physiological state of body tissues.—Authors' Abst.

Catalase studies in adrenalectomized guinea pigs and in Addison's disease (Katalasestudien bei nebennierenextirpierten Meerschweinchen und Morbus Addison). Oefelein, F. and H. Trautwein, Arch. f. exper. Path. u. Pharmakol. **165**: 131. 1932.

An increase in catalase index followed adrenal extirpation in 16 guinea pigs. Two sham-operated controls showed no significant change. The average catalase index of five patients with Addison's disease was definitely higher than the normal average. The index is suggested as a criterion of adrenal insufficiency.—R. L. Zwemer.

Studies on adrenalectomized guinea pigs (Studien an nebennierenextirpierten Meerschweinchen). Oefelein, F. and H. Trautwein, Arch. f. exper. Path. u. Pharmakol. **165**: 138. 1932.

Adrenalectomy was followed by a marked increase in respiratory rate, respiratory water output and carbon dioxide output. These reached their maxima on the sixth or seventh day after operation, shortly before death (five guinea pigs). Two additional animals showed diminished urine output in spite of daily saline or glucose injection. In four guinea pigs there was a terminal rise in NPN and globulin. The authors correlate these data with a previously reported increased catalase index as evidence for increased cell respiration and suggest that the latter is influenced by the adrenal.—R. L. Zwemer.

Sympathetic tumors of the adrenal medulla. Scott, E., Marguerite Oliver and Mary Oliver, Am. J. Cancer **17**: 396. 1933.

One hundred and fifty-eight cases of tumors with origin in one or both adrenal medullas have been collected from the literature and classified on the basis of their structural differentiation. Four cases of sympathicoblastomas or undifferentiated sympathetic tumors of the adrenal are reported from the authors' laboratories. A scheme of classification for sympathetic tumors is presented, based on the present conception of the histogenesis of the neuroblast and spongioblast, and the study of the histological picture in the authors' cases: Class I: Completely undifferentiated sympathicoblastomata. Sympathogoniomata with the most immature or medulloblast-cell type, characterized by large, round nuclei, slight cytoplasm, and a tendency to clump themselves in "pseudorosettes." Sympathoglioblastomata with (1) slightly differentiated cells representing the sympathoblast, an immature cell in the spongioblast or supporting series, displaying a tendency to the formation of blepharoblasts and rosettes having "internal limiting membranes," and (2) the immature neuroblast of the bipolar type. Class II: Partially differentiated sympathetic tumors. Sympathetic neuroblastomata with the predominant cell of the unipolar neuroblast type. Spongioblastomata or lemmoblastomata with the spongioblast or capsular cell conspicuous in its proliferation. Chromaffinoblastomata with tumor cells possessing chromaffin-staining properties. Class III: Completely differentiated tumors of the sympathetic. Ganglioneuromata. Chromaffinomata or paraganglionata. The younger the patient, the more undifferentiated the tumor elements. The more undifferentiated the tumor, the greater the number of metastases and the greater the degree of malignancy. The Pepper type of adrenal tumor, originating in either or both adrenals and characterized by huge metastases to the liver, is found only among the completely undifferentiated sympathicoblastomas and occurs among younger children than does the Hutchison type, originating in either adrenal and characterized by metastases to the skull bones, eye orbit, and ribs. The early appearance of these undifferentiated tumors, especially of the Pepper type, suggests a congenital and heterotopic origin. There is evidence, however, for a genuine metastasis as well.

—Authors' Abst.

Effect of incretions on the motility of mammalian sperms (Die Wirkung der inkretorischen Stoffe auf die Bewegung von Säugetierspermien). Becher, H., Anat. Anz. **71**: 191. 1931.

Fresh bull sperms, suspended in Ringer's solution, were treated with various hormonal substances and the variations in motility were noted. On this basis the incretions could be divided into three groups: (1) a group, including follicular fluid (from ripe follicles of cow ovaries) and thyroxine, which stimulate and prolong the duration of movement; (2) a group, including adrenaline, progynon, hypophysin and insulin, which inhibit the amount and duration of motion, and (3) a group which had no effect on sperm motility, the only representative being adrenaline. Thus the influence on the motility of sperms may be used to test quickly the potency of many hormonal extracts and even to standardize them. It also has the advantage that test material is easily obtainable.—A. T. R.

Genetic factors in the response of feather follicles to thyroxin and theelin. Danforth, C. H., J. Exper. Zoöl. **65**: 183. 1933.

Fowls of six different genotypes were treated with thyroxine and theelin. The two drugs seem to have qualitatively similar effects on such feathers as are strictly comparable, but there are marked racial and regional differences in response. Depending on the genotype, the same dosage of thyroxine may produce no obvious effect, may cause white feathers to be replaced by yellow, yellow feathers by white ones, black by yellow, etc. These diverse results are readily explainable on the assumption that thyroxine and each of the significant genes tend to have predictable effects, the action of thyroxine, however, being conditioned by the genic complex. For example, genes homozygous for yellow do not ordinarily react with thyroxine, but genes for yellow and black furnish a combination which does react, and the gene for dominant white, when present, although not preventing this reaction, completely suppresses its effect. Since such responses as are induced by theelin and thyroxine appear to be really determined by the genotype, the hormones may be regarded simply as factors in an internal environment to which certain tissues in some species have evolved

specific responses. Phylogenetically, the hormones appear to be older than many of the present-day reactions to them. These reactions may be strikingly dissimilar in different races of the same species.—Author's Abst.

Evidence for a neurohumoral control of fish melanophores. Mills, Sylvia M., J. Exper. Zoöl. **64:** 245. 1932.

These experiments with Fundulus heteroclitus were designed to test the theory that melanophore nerve endings in fishes secrete substances so close to the cells they supply as to cause them to react. These substances are considered to be responsible for the reactions of denervated melanophores which they reach by transfusion. It was found that the responses of melanophores in a denervated area following a change in the shade of the fish did not take place simultaneously. They started at the periphery of the denervated area and gradually spread to its center. This indicates that secretions affecting the melanophores were not produced in distinct glands and carried in the blood stream, but rather that they were formed in the surrounding tissues and reached the denervated area by a gradual spread. Pallor due to shock affected the cells of a denervated area rapidly and uniformly. Denervated cells surrounded by melanophores responding to mechanical or electrical stimulation reacted in the same way as the innervated cells, though more slowly. These reactions of denervated melanophores also occurred in tails isolated from the body by a cut posterior to the anal fin. They could not therefore he caused by secretions from glands anterior to this cut and distributed in the blood stream.—Author's Abst.

Intracranial ovarian grafts in normal male guinea pigs and ones which had been previously castrated (Greffe ovarienne intracérébrale chez des Cobayes males entiers et préalablement chatrés). Athias, M. and A. Guimarais, Comp. rend. Soc. de biol. **113:** 733. 1933.

In nine normal guinea pigs the grafts had no effect. In 18 animals castrated before the grafts were introduced, five showed evidence of feminization. This small number of takes indicated that the intracranial position was not as favorable as the renal for ovarian grafts.—J. C. D.

The Friedman modification of the Aschheim-Zondek test for the diagnosis of pregnancy. Best, C. H. and E. W. McHenry, Canad. M. A. J. **28:** 599. 1933.

Two rabbits were used for each test. The first morning sample of urine was employed. On the afternoon of the first day and on the morning of the second day the rabbits were given 8 cc. of urine intravenously. On the morning of the third day they were killed and the ovaries examined macroscopically. One or more corpora hemorrhagica were considered to indicate a positive result. Of 538 tests for which clinical information is available 251 were positive with 1.6% errors and 287 were negative, with 2.1% errors. Cases of ectopic pregnancy, hydatiform mole and incomplete abortion giving positive results were not considered as errors. Possibly three ectopic cases giving negative results should be classed as errors, raising the percentage error for negative cases to 2.4. A large number of the tests were carried out on urine from patients less than eight weeks pregnant.—A. T. C.

Effect of Roentgen rays on the ovaries and ganglion cervicale uteri (Zusammenwirken der Inkrete). Blotevogel, W., Anat. Anz. **72:** 196. 1931.

Eleven mice, under ether anesthesia, were so operated upon that each ovary could be directly irradiated. Doses ranged from 5 MA.-70 volts to 10 MA.-73 volts, applied at distances varying from 11 to 176 cm. Six weeks later the animals were killed and ovaries and nerve cells of ganglion cervicale uteri were studied and compared with one control animal. Quantitative changes in the ovary were determined by counting the number of atretic follicles. Increasing doses resulted in an increasing number of degenerating follicles until 10 MA.-70 volts at 44 cm. or higher, when all the follicles became atretic. Follicles without a cavity appeared to undergo atresia sooner than those with a cavity. The nerve cells of ganglion cervicale uteri decrease in size to the same extent as occurs when ovaries are removed. Six additional animals were given 10 MA.-73 volts at distances varying from 11 to 88 cm. and then subsequently given three 50-unit doses of progynon (Schering-Kahlbaum), a sex hormone, at intervals of two days, without any noticeable restorative effect on the ovaries. The sympathetic ganglion cells, however, had increased in size.—A. T. R.

The female sexual hormone; comparative investigation of theelol, emmenin and follicular hormone hydrate (Vergleichende Untersuchung von Theelol, Emmenin und Follikelhormonhydrat. Untersuchungen über das weibliche Sexualhormon). Butenandt, A. and J. S. L. Brown, Ztschr. f. physiol. Chem. **216**: 49. 1933. Abst., Chem. Absts. **27**: 2719.

The slight disparities in activity and properties between Doisy's theelol, Browne's emmenin and Butenandt's hormone hydrate, reported in previous literature, had suggested the possibility of isomerism and non-identity. A comparison of all three in the same laboratory by the same technic now establishes their identity. Satisfactory agreement was obtained in melting point, mixed melting point, optical rotation, ultra-violet absorption and physiological activity. Triacetates preparation from theelol and hormone hydrate were identical.

The development and hormonal content of fetal horse gonads. Cole, H. H., G. H. Hart, W. R. Lyons and H. R. Catchpole, Anat. Rec. **56**: 275. 1933.

Gonads from about 300 horse fetuses have been studied, particular attention being given to the correlation of the condition of the fetal gonads with that of the maternal ovaries and with the hormonal concentrations in the mare. The fetal gonads of both sexes reach a maximum size at 45 to 65 cm. C.-R. length, at which time they exceed the maternal ovaries in size. This large size is due to an interstitial cell overgrowth the height of which is attained some little time after the gonad-stimulating hormone is no longer recognizable in the maternal blood stream. Toward the end of intra-uterine life most of the interstitial cells degenerate and there is a consequent reduction in the size of the gonads. Gonads, blood, and livers from fetuses during the second half of pregnancy contain considerable quantities of oestrin. Thus it is felt that the fetus must be considered as one possible source of the large amounts of oestrin excreted in the maternal urine.—Authors' Abst.

Experimental genital crises in new born kittens (Crise génitale expérimentale chez la Chatte nouveau-née). Courrier, R. and G. Gros, Compt. rend. Soc. de biol. **110**: 1021. 1932.

There was a marked development in the genital tract, particularly the uterine glands, of new born kittens whose mothers received repeated injections of folliculin during pregnancy. If the folliculin was injected directly into the new born kitten, there was no such picture of overactivity.—J. C. D.

The uterus as an organ of internal secretion (Der Uterus als inner sekretorisches). Fellner, O. O., Arch. f. d. ges. Physiol. **231**: 410. 1932. Abst., Chem. Abst. **27**: 3508.

A substance with chemical and physiological properties similar to those of the anterior lobes of the pituitary hormone is derivable from the decidua, uterine mucosa and placenta. This hormone is considered as playing an important rôle in the female organism.

Thyroid and ovary (Schilddrüse und Ovarium). Abelin, I. and E. Wiedner, Arch. f. exper. Path. u. Pharmakol. **166**: 584. 1932.

The function of the ovaries is influenced by the anterior pituitary and the thyroid glands in an antagonistic way. The first stimulates its function, while the second inhibits it. With the administration of thyroxine or thyroid gland extract the estrus in rats can be interrupted or suppressed. The inhibiting effect of the thyroxine on the estrus is diminished, when prolan (anterior pituitary extract) is administered along with it. Folliculin acts similarly to prolan but is more effective. With the administration of folliculin the oestrus cycle can be retained most of the time in spite of the prolonged administration of thyroxine. With the aid of certain dietary changes the inhibiting effect of the thyroxine on the ovarian function as well as the other toxic symptoms caused by the administration of thyroxine, can be removed. Two food mixtures are described. The preservation of the function of the genitalia is found to be of importance in the control of hyperthyroidism. Eighteen rats were used in these experiments. The findings are summarized in four tables.—A. Rudy.

On the pregnancy reaction in mares (Über Graviditätsreaktion bei der Stute). Glud, P., K. Pedersen-Bjergaard and K. Portman, Endokrinologie, **13**: 21. 1933.

In a study of the prolan content of the blood serum and the oestrin content of the urine of 27 non-pregnant and 29 pregnant mares, the authors found the following: (1) The non-pregnant mare shows no demonstrable quantity of prolan A and B in 0.5 to 5.0 cc. of blood serum injected into infantile mice in the course of two days. (2) From the 42nd to the 125th day of pregnancy, there is a steady increase in the amount of prolan A and B in the blood serum. Thereafter, it is no longer demonstrable in these quantities of blood serum injected into infantile mice. (3) Simultaneously with the decrease of prolan A and B in the blood serum of the pregnant mare, there is an increase in oestrin excretion so that on the 136th day of pregnancy a liter of urine contains as much as 22,500 mouse units of the hormone. The urine of the non-pregnant mare contains no more than 60 mouse units of the hormone per liter. The late appearance of prolan A and B in the blood and of oestrin in the urine of the pregnant mare, in contrast with the early appearance of these hormones in the pregnant human, is probably due to the late imbedment of the ovum of the mare in the uterine mucosa. The authors found that a diagnosis of pregnancy in the mare by means of injecting a total of 0.5 to 5.0 cc. of blood serum into infantile mice (Aschheim-Zondek reaction) or a total of 1.8 cc. of urine into castrated adult mice (Allen-Doisy reaction) can be made on or after the 42nd day of pregnancy when bimanual examination is still inconclusive.—C. Mazer

Ovarian hormone and traumatic stimulation of monkey's cervix to a condition resembling early cancer. Overholser, M. D. and E. Allen, Proc. Soc. Exper. Biol. & Med. **30**: 1322. 1933.

Nine adult female Macacus rhesus monkeys were used. Cervical trauma was produced by scissor cuts at 7 to 10-day intervals. In addition, a metal clip was clamped on the cervix of some animals. Subcutaneous injections of hormone were made twice daily, morning and evening, as a rule. The daily dose of ovarian follicular hormone given as theelin or amniotin, ranged from 50 to 100 rat units. Four of the animals also received injections of corpus luteum hormone during the latter part of the theelin injections. Six ovariectomized animals received cervical trauma and injections of ovarian follicular hormone, ranging in total dosage from 1,535 to 5,490 rat units over time periods ranging from 16 to 90 days. The cervices of these animals showed various degrees of atypical epithelial hyperplasia occurring at the junction of the stratified squamous and glandular epithelium. In many regions columnar epithelium was surrounded by stratified squamous. One animal showed early but essential features of infiltrating epidermoid carcinoma in an ulcerating area. One ovariectomized animal receiving hormone injections only for a period of 51 days, showed a close approximation to established cervical cancer. One animal with ovaries intact receiving only cervical trauma for 119 days, showed a few areas of epidermization of the cervical glands. An ovariectomized animal receiving only cervical trauma for 86 days showed slight atypical downgrowth.

—M. D. Overholser.

Treatment of disturbances of the estrual cycle with sex hormones (Ueber Behandlung der Stoerungen des Brunstzyklus mit Geschlechtshormonen). Gostimirovic, D. and G. O. Kraemer, Endokrinologie, **13**: 16. 1933.

Of 98 white mice 28 were found to have irregular cycles, with smears in the resting phase over periods from 43 to 59 days. Into 11 of these follicular hormone in oil solution was injected, 300 mouse units in 5 doses within six days. Although 3 died, the other 8 showed estrus of 9 to 15 days, beginning about 70 hours after treatment. A second estrus occurred 18 to 30 days later. After 39 days from the first estrus 7 of these mice received 3 weekly doses of 140 units of the same solution. In 5 mice estrus occurred with average duration of 21 days. To 12 mice daily doses of 0.3 mouse unit of prolan were given, followed by estrus in 3 to 5 days. No further estrus occurred later. Then 11 mice received weekly injections of 0.7 mouse units of prolan. Of these 2 died, and 5 had improved estrual cycles. Controls were observed, using 5 of the mice, and these showed occasional cycles. The authors conclude that sexually mature white mice with disturbed estrual cycles resemble immature white mice in that neither folicular hormone nor prolan can cause persistence of regular cycles.

—E. L. Sevringhaus.

The sexual cycle in the human female as revealed by vaginal smears. Papanicolaou, G. N., Am. J. Anat. **52:** 519. 1933.

The vaginal smear method has been used in a study of the human female sex cycle. Daily smears from 13 normal women have been collected through two to three consecutive menstrual periods. Four distinct phases are described: the congestive or menstrual (first to seventh day); the follicular or copulative (eighth to twelfth day); the proliferative (thirteenth to seventeenth day), and the premenstrual (eighteenth to first day). Each phase shows cellular changes in the vaginal fluid. An ovulative reaction in the smear follows the follicular phase, usually 12 to 13 days after onset of menstruation. Seventeen operated cases were used to determine the relation of the ovaries to the various vaginal smear stages. Changes in the vaginal fluid during gestation and after parturition are briefly described. Post-partum smears resemble stage III, as recorded for the guinea pigs. The human cycle is analyzed and a new classification introduced. The short menstrual type of 21 days, though rare, corresponds closely to the general mammalian standard. The normal 28-day period shows retardation in the follicular growth rate, causing a reversal of certain vaginal smear stages and a secondary expression in the uterine cycle.—Author's Abst.

The production of deciduomata in spayed immature rats after oestrin and progestin treatment. Shelesnyak, M. C., Anat. Rec. **56:** 211. 1933.

In order to test the physiological capacity of the infantile uterus to form deciduomata, a series of 56 immature rats were spayed and treated with varying amounts (from 4 to 100 r.u.) of oestrin (Amniotin, Squibb) for 4 days. After the preliminary injections of oestrin, alcohol extracts of hog corpora lutea (from 4 to 84 grams—equivalent of fresh tissue) was administered for 8 days. The uteri were stimulated by modified silk thread loops on the fourth or fifth day of progestin treatment. The results show that such treatment develops a trauma-sensitive endometrium, and decidual growths are formed. Although 52% of the animals (each of which received a different dosage of oestrin and progestin) show some response, macroscopic growths were few (6) and limited to animals which were given the lesser quantities of substances.—Author's Abst.

The treatment of menstrual disorders by the injection of blood from pregnant donors; a preliminary report. Witherspoon, J. T., New Orleans M. & S. J. **86:** 85. 1933.

A preliminary report of treatment of four gynecological disorders by sex-hormone therapy. Twenty-five cases of functional disorders of menstruation are presented: (1) Idiopathic or functional uterine bleeding, or hyperplasia of the endometrium; (2) Amenorrhea; (3) Primary dysmenorrhea; and (4) Menopausal disturbances. The patients were treated for 18 months and the same technique used in all. Ten cc. of blood was taken from the cubital vein of a woman in the early months of pregnancy and injected immediately into the buttocks of the patient. Injections were given at weekly intervals when the treatment was indicated. In the first group all 8 patients reported that the hemorrhage was successfully stopped. In 6 of the 12 patients in the second group the menstrual flow returned. No definite improvement could be noted in the cases of dysmenorrhea, but excellent results were obtained in the 2 cases of menopausal disturbances. The author feels that any new method of therapy dealing with disorders of menstruation must fulfill three tests: (1) that the restored uterine hemorrhage is true menstrual flow and not merely menstruation without ovulation; (2) that the menstrual cycle can be regulated to its normal periodicity in order to make future conception safe, and (3) that the menstrual cycle, restored to its normal rhythm, will remain a permanent function.—Author's Abst.

Effect of cortical hormone in preventing extreme drop in colonic temperature displayed by hypophysectomized rats upon exposure to cold with preliminary observations upon the effect of hypophyseal and other hormones. Baird, P. C., Elizabeth Cloney and F. Albright, Am. J. Physiol. **104:** 489. 1933.

Within 24 hours following hypophysectomy a great loss of tolerance for cold temperatures occurred in rats. This tolerance decreased only slightly in subsequent weeks. At an average cold room temperature of 3.6° C. 13 hypophysectomized rats in 5 hours underwent an average drop of 11.5° C. in colonic

temperature. Eleven normal rats tolerated the same average temperature for an average of 14.5 hours with a drop of only 1.4° C. in colonic temperature. Hypophysectomized rats recovered from colonic temperatures as low as 16° C. (60.8° F.). Cortin almost completely restored the resistance of five hypophysectomized rats to cold temperatures (3° C.). Thyroxine in toxic doses increased the tolerance of a hypophysectomized rat to cold temperatures. The thyrotropic hormone of the pituitary likewise almost restored the tolerance of hypophysectomized rats to cold temperatures. Theelin, adrenaline, normal saline, 5% glucose, the pituitary growth hormone together with the pituitary gonad-stimulating hormone, the gonad-stimulating hormone of pregnancy urine, and pituitrin did not influence the resistance of hypophysectomized rats to cold temperatures. Gonadectomy was followed within two months by a diminution of resistance to cold temperatures (two cases). Two thyroidectomized rats were approximately as resistant as normal rats to cold temperatures up to 26 days following thyroidectomy.—R. G. H.

Further studies on the anterior pituitary-like hormone with special reference to irregular uterine bleeding. Campbell, A. D., Canad. M. A. J. **27:** 347. 1932.

The several types of irregular uterine bleeding may be distinguished by their menstrual histories. In selecting cases for treatment with the anterior-pituitary-like principle correct diagnosis is absolutely essential. The organs in the pelvis must be palpably normal and the presence of neoplasms of the uterus must be excluded. Menorrhagia and metrorrhagia due to inflammatory disease are aggravated. Metropathia hemorrhagica responds particularly well. Pain is taken to signify that the musculature has returned to normal tone, and that the hyperplastic endometrium is being rapidly expelled. The duration of the treatment varies. Some patients have remained cyclic during two years of observation after treatment. Response is not so consistent in metrorrhagia of puberty, and treatment is followed by periods of amenorrhea. Menopausal symptoms are alleviated. Mastalgia, if accompanied by disturbed menstrual cycles, frequently subsides. No permanent improvement has been obtained in simple polymenorrhea. The symptoms of dysmenorrhea are intensified. There is no effect in pregnancy, and no effect on normal menstrual cycles as regards interval, amplitude, or duration; no local or constitutional symptoms are observed. It is considered that the effect of A-P-L is to cause the ovary to resume a complete and balanced endocrine activity in place of one that is unbalanced and incomplete.—A. T. C.

Studies of visual fields in functional headaches of pituitary origin. Cushman, Beulah, J. A. M. A. **101:** 837. 1933. Abst., A. M. A.

While making a study of headaches which had been treated in the past six years with the roentgen rays and glandular extracts, the author noticed that the similarities of the visual field were strikingly alike. In a few cases in which correction of the refractive error did not relieve the cephalalgia, a study made with the aid of the internist, the roentgenologist and visual fields led to the belief that these headaches are of pituitary origin. From this study, the author concludes that certain periodic attacks of headaches and discomfort of the eyes simulating ciliary spasm may be due to dysfunction of the organically sound pituitary gland or to distention of its capsule by physiologic hypertrophy. The majority of the visual fields show a contraction of the superior temporal quadrant for color and varying changes in the form fields.

The occurrence of thyroid gland substances in the blood after the anterior pituitary has exerted its effect (Auftreten von Schilddrüsenstoffen im Blut nach Wirkung von Hypophysenvorderlappen. Prüfung der Wirksamkeit im Kaulquappenversuch). Grab, W., Arch. f. exper. Path, u. Pharmakol. **168:** 715. 1932.

Prolonged parenteral administration of anterior pituitary extracts to animals causes the occurrence in their blood of growth-stimulating substances. Its presence is demonstrated by the positive Gudernatsch reaction, which consists in the acceleration of the metamorphosis of the tadpole. The analogy of these substances with the natural thyroid gland substances is discussed. The experiments were carried out with the blood of five dogs and two cats treated for some time with anterior pituitary extract. For each experiment three groups of tadpoles were used. The blood was quickly dried and powdered and 100 mg. of this powder was added to the fish food. On group received in its food the dried

powdered blood of the treated animals, the second group received the blood of non-treated animals, and the third group just fish food without the powdered blood. Control experiments were also carried out on two groups of tadpoles by adding to the food of one group dry powdered blood of animals treated with inactive anterior pituitary extract, and to the food of the second group the dry powder of the anterior pituitary extract only. After about eight to ten days the tadpoles were killed and examined for size and grade of development. A picture illustrating the difference in the rate of the development of the tadpoles in these experiments is given.—A. Rudy.

Secretion of hormones of anterior lobe in urine in endocrine disturbances (Über die Ausscheidung der Hormone des Hypophysenvorderlappens im Harn bei endokrinen Erkrankungen). Hirsch-Hoffmann, H. U., Klin. Wchnschr. **11**: 94. 1932.

The author has striven to prove the presence of the Aschheim-Zondek reaction in cases of known (clinically diagnosed) and suspected hypophyseal disturbances. He has gathered material for his article from 37 cases of the Noone and Schottmüller clinics, 10 of which he recites in detail. Of these 10, seven were male, three female. The test was carried out through injection of infantile mice with 2 cm. of early urine from the sufferers, and 100 hours after the first injection the results of the reaction were observed. In the 10 cases discussed, whether male or female, with established or suspected diagnosis of hypophyseal disease, a positive Aschheim-Zondek reaction was noted. Despite reservations, the author concludes, that increased anterior lobe hormone secretion frequently appears in diseases in which hypophyseal participation is either positive or suspected.—G. A. Wyeth.

The relationship of the anterior pituitary to the thyroid (Über die Beziehungen zwischen Hypophysenvorderlappen und Schilddrüse). Hohlweg, W. and K. Junkmann, Arch. f. d. ges. Physiol. **232**: 148. 1933.

Thyroidectomy in rats produced changes in the cells of the anterior pituitary which were similar to those produced by castration. There were slight morphological differences. Thyroidectomized young female rats were injected with anterior pituitary sex hormone. They reacted like the normal controls, with the production of oestrus and changes in the ovaries. The pituitaries of fifteen thyroidectomized female rats were implanted in young female rats. As a control the pituitaries of five ovariectomized rats were used. The former produced no changes; whereas the controls produced oestrus, large follicles and corpora lutea. Moreover, injections of progynon in thyroidectomized young female rats did not prevent the formation of the "thyroidectomy cells" in the pituitary, whereas such injections did prevent the formation of "castration cells" in ovariectomized rats. Therefore, "thyroidectomy cells" are functionally different from "castration cells." Feeding of desiccated thyroid or the injection of synthetic thyroxine prevented the development of "thyroidectomy cells." Potassium iodide and diiodotyrosin did not possess this property. The thyreotropic activity of the pituitary was tested on young guinea-pigs, using the changes in the epithelium and the disappearance of colloid from the thyroid follicle as criteria. By this method the thyreotropic activity of the pituitary was found to be the same, whether the pituitary was derived from a thyroidectomized animal, a normal animal or an ovariectomized animal. On the other hand, the thyreotropic activity of the pituitary derived from animals treated with thyroxine was one-fourth of that of the pituitary derived from untreated animals. The thyreotropic activity of the pituitary has a similar relation to the thyroid as the gonadotropic activity of the pituitary has to the gonads.

—J. Lerman.

Hypophysis and glycogen in toads (Hipófisis y glucógeno en el sapo). Houssay, B. A., E. di Benedetto and P. Mazzocco, Rev. Soc. argent. de biol. **9**: 4. 1933.

Blood sugar was lower in toads (Bufo arenarum) after hypophysectomy or extirpation of the anterior pituitary lobe. A daily subcutaneous implantation of one glandular lobe partially restored the normal blood sugar level. Posterior pituitary lobe produced a similar but less marked effect. Liver glycogen was considerably reduced in hypophysectomized toads and in those whose anterior lobe had been removed; the decrease was most pronounced the third week after operation. Implantation of anterior lobe compensated in part for this decrease; posterior lobe acted in a similar way but was less active. Muscle glycogen also

diminished gradually after hypophysectomy and anterior lobe extirpation, but the relative and absolute decrease was less than that observed in liver glycogen. Anterior lobe implantation and in a lesser degree posterior lobe implantation prevented or diminished the loss of muscle glycogen.—J. T. L.

Hypophysis and pancreatic diabetes in batrachians and reptiles (Hipófisis y diabetes pancreática en los batracios y los reptiles). Houssay, B. A. and A. Biasotti, Rev. Soc. argent. de biol. **9**: 29. 1933.

Hypophysectomy prevented hyperglycemia after pancreatectomy in Leptodactylus ocellatus, Bufo d'Orbigny, Ceratophrys ornata and Ophis merremii. Implantation of the anterior pituitary lobe produced diabetes in hypophysectomized, pancreatectomized batrachians. In Ophis merremii implantation of 1 to 5 lobes daily of anterior pituitary from the same species, B. arenarum and steers or the injection of Evans and Simpson's anterior lobe extract did not produce diabetes after pancreatectomy and hypophysectomy. Extirpation of the lungs, thyroid, testicle, kidneys and the digestive tract did not prevent hyperglycemia after implantation of anterior lobe in hypophysectomized, pancreatectomized Bufo arenarum. By adsorption with kaolin and elusion by alcohol 66% it was possible to extract from human urine a substance that increased the blood sugar in hypophysectomized, pancreatectomized toads. Urine of diabetic patients was usually more active than that of normal individuals and patients suffering from several other complaints.—J. T. L.

The diabetic effects of extracts of the anterior lobe of the hypophysis in dogs Action diabétogène des extraits antéro-hypophysaires chez le Chien). Houssay, B. A., A. Biasotti, E. di Benedetto and C. T. Rietti, Compt. rend. Soc. de biol. **112**: 494. 1933.

Normal dogs (22), 3 without hypophyses and 3 without thyroids, were injected with Evans-Simpson alkaline extract of anterior lobe in daily doses of 7 cc. per kilo. After the fifth day they developed hyperglycemia and other abnormal changes. The 19 controls injected with thyroid, posterior lobe, or adrenine showed no such changes.—J. C. D.

Hypophyseal cachexia (Über hypophysäre Kachexie). Hürthle, R., Med. Klin. **28**: 1637. 1932. Abst., J. Nerv. & Ment. Dis. **78**: 417.

Hypophyseal cachexia is not as rare as is generally believed, according to this study. Five patients are reported. The author is convinced that somewhat atypical forms may develop in women after gestation. "Nervous disturbances," lack of appetite, emaciation, loss of hair, and menstrual and gastric disturbances were the chief complaints. Three of the women had low blood pressure and four stated that the disorders had set in following pregnancy. All five were of the asthenic type. This structural type is somewhat predisposed to this disorder. Prolonged treatment with a preparation of the anterior hypophysis and with insulin effected considerable improvement in all five patients, and the author considers the efficacy of this treatment proof that the patients had a mild form of hypophyseal cachexia. He also observed a severe case of hypophyseal cachexia and he reports this clinical history in detail.

Quantitative variation of the anterior pituitary hormone, "APH-B," in the blood during pregnancy. Kennedy, W. P., Quart. J. Exper. Physiol. **23**: 367. 1933.

Quantitative tests of the anterior pituitary hormone B in the blood plasma of 75 normal women show that the amount increases steadily during pregnancy till after the 30th week, when the increase is more variable. The range is approximately from 1,000 mouse units per litre at the 3rd week to 11,000 at the 30th.—Author's Abst.

The mouse unit of anterior pituitary hormone B. Kennedy, W. P., Quart. J. Exper. Physiol. **23**: 373. 1933.

A method of bio-assay of the luteinizing hormone of the anterior pituitary (B hormone) is described. The amount required to produce the chosen limiting reaction is ten times greater when given in one dose than when split into six parts. The differential production of corpora lutea and haemorrhagic follicles does not depend on dosage. The mouse unit of anterior pituitary hormone B (Prolan B) is defined as the amount which, divided into six doses, and injected

intraperitoneally into 10 female mice exactly three weeks old, over a period of 36 hours, will produce haemorrhagic follicles and/or corpora lutea in 50% of the animals 100 hours from the first injection.—Author's Abst.

A specific hormone of carbohydrate metabolism antagonistic to insulin found in the anterior hypophysis (Experimentelle Untersuchungen über ein spezifisch auf den Kohlehydratstoffwechsel eingestelltes, dem Insulin entgegengerichtetes Hormon des Hypophysenvorderlappens). Lucke, H., E. R. Heydemann and Ruth Hechler, Ztschr. f. d. ges. exper. Med. **88:** 65. 1933. Abst., Chem. Absts. **27:** 3510.

An extract of the anterior pituitary produces hyperglycemia in normal men and dogs and antagonizes insulin hypoglycemia. The disturbances of carbohydrate metabolism noted in animals with hypophyseal insufficiency can be corrected by the extract, especially the hypersensitivity to insulin. The hormone functions with adrenaline as an antagonist to insulin in the regulation of carbohydrate metabolism.

The action of pituitary extracts on the kidney. Macdonald, A. D., Quart. J. Exper. Physiol. **23:** 319. 1933.

The action of posterior pituitary extracts on the renal vessels is not dilator, as usually stated. In the pig marked contraction has been found. In the cat, rabbit, sheep, and cow the plain muscle of the arteries is scarcely affected by pituitary extracts, though it is sensitive to other drugs. It is concluded from experiments on the cat, dog, rabbit, and man that the diuretic action is associated with rise of blood-pressure, and is always followed by anti-diuresis.
—W. P. Kennedy.

The antagonistic effect of alcohol on pituitary hyperglycaemia. Murray, M. M., J. Physiol. **77:** 247. 1932.

Alcohol administered to cats by mouth or intravenously, so that a concentration of over 100 mg./100 cc. of blood was attained, prevented the rise of blood sugar which normally resulted from the injection of pituitrin.
—Author's Summary.

Increased excretion of anterior pituitary lobe hormone "prolan" in the urine during the involutional period and senility (Vermehrte Ausscheidung von Hypophysenvorderlappenhormon Prolan im Harne in der Involutionsperiode bzw im Senium). Österreicher, W., Klin. Wchnschr. **11:** 813. 1932.

In a study of the anterior pituitary sex hormone (prolan) content of the urine of 44 normal and psychopathic women ranging in age from 52 to 91 years, Oesterreicher found an excess prolan excretion (80 to 330 mouse units per liter) in 39. In the majority of the cases he found prolan A; in some prolan B was demonstrable. Castrates show a similar increase in prolan excretion. The author concludes that the invariable increase of prolan excretion in cases of genital carcinoma of menopausal women may partly be due to the age of the patients and not to the presence of malignancy. Whether the increased excretion of the hormone is due to a genuine hyperfunction of the anterior pituitary lobe or a lack of utilization of an otherwise normal supply is not known.
—C. Mazer.

Ketosis in the pancreatic and phlorrhizin diabetes of hypophysectomized dogs. Rietti, C. T., J. Physiol. **77:** 92. 1932.

Ketone elimination was notably less (1:3.6) in the pancreatic diabetes of hypophysectomized dogs than in the controls. It bore a relationship to the level of the blood sugar. It was intermediate in animals with lesions of the tuber cinereum. The ketone elimination was much less (1:17) in the phlorhizin diabetes of hypophysectomized fasting dogs than in the normal controls; in thyroidectomized animals, in those without the posterior pituitary lobe, and those with lesions of the tuber cinereum ketone elimination was greater than in the controls. In hypophysectomized dogs on meat, sugar or fat diets the ketone elimination in phlorhizin diabetes was always less than in the corresponding controls. The intake of sugar diminishes the ketone elimination in the controls, but in the hypophysectomized there is a slight rise. The ketone elimination of hypophysectomized fed dogs under phlorhizin did not increase as much as did the glycosuria during meat intake. Pituitary insufficiency always diminished the urinary elimination of ketone bodies.—Author's Summary.